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LONG-TERM FOLLOW-UP STUDY OF PENICILLIN-TREATED SUBACUTE BACTERIAL ENDOCARDITIS*

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SINCE 1944, when penicillin became available in quantity, subacute bacterial endocarditis has moved from the category of an almost uniformly fatal disorder to the ranks of curable disease. Among the many well documented papers[1-14] supporting the efficacy of treatment is an earlier report from this clinic.[15] During the past five years, the original group of patients described has been considerably augmented. It is the purpose of this paper to report on the altered clinical pattern seen in these patients since the advent of penicillin therapy, and the effect of this therapy on long-term results.

CLINICAL MATERIAL

From 1944 through 1947, a period arbitrarily chosen to provide at least a one-year follow-up study on the most recent cases, 60 patients with proved subacute bacterial endocarditis were admitted to this hospital. Diagnosis was substantiated by two positive blood cultures, the association of two or more classic clinical signs with at least one positive blood culture, or post-mortem examination. Patients were selected for study who had received 200,000 units or more of penicillin a day for at least ten days and who either were followed for over a year after therapy or came to autopsy. Thirty-eight patients met these criteria, and the remaining 22 were excluded from further analysis.

Reinfections

Two of the 38 patients were retreated for reinfection, fifteen and sixteen months, respectively, after bacteriologic cure of the initial infection. During the interim, both were followed in this clinic, where they were noted to be free of the stigmas of the smoldering or "bacteria-free" stage of bacterial endocarditis.[16] Thus 40 episodes of treated subacute bacterial endocarditis in 38 patients were analyzed in this study.

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OBSERVATIONS

Etiologic and Predisposing Factors

The etiologic and predisposing factors are presented in Table 1. The average age at onset for the group was thirty-four years. Twenty were females, and 18 males. Eighty-three per cent had pre-existing rheumatic valvular disease. Among the congenital defects present in 6 patients, there were 5 cases of patent ductus arteriosus, 1 of interventricular septal defect and 1 of a bicuspid aortic valve. Dental extractions or major fillings without associated penicillin prophylaxis had been carried out in 38 per cent of the patients within the immediate weeks before the development of endocarditis. Upper respiratory infections, furunculosis, pyelitis, appendicitis and cystitis preceded endocarditis in 6 other cases, whereas in 20 no antecedent infection could be implicated. The alpha-hemolytic streptococcus was the responsible organism in 33 of the 40 treated episodes. There were 2 double infections; an infection due to *Alcaligenes faecalis* developed in 1 patient during penicillin treatment for an endocarditis caused by alpha-hemolytic streptococcus; the other patient had endocarditis due to both alpha-hemolytic streptococcus and *Escherichia coli*. These organisms were isolated both from the blood during life and from the heart valves at autopsy in each of these patients.

Significant Clinical Findings

The clinical findings are shown in Table 2. The average duration of infection, as indicated by onset of symptoms before admission, was three and a half months, with a range extending from two days to one year. Symptoms of infection were noted by all but 1 patient. Ninety-three per cent had a history of a murmur before infection developed, and in all the murmur remained essentially unchanged during the hospital stay. Sixty-four per cent of the patients who subsequently survived had a fever on admission, and all but 1 of those in the fatal cases were febrile at that time. Nine of

the 12 patients who died had symptoms of congestive failure before the start of treatment, whereas such symptoms were present in only 3 of the 28 who recovered. Arthralgia, splenomegaly and embolic phenomena were slightly more common among the fatal cases. The presence of albumin in the urine, with red cells and casts in the sediment, was more common among those who subsequently did not survive.

Fourteen patients were tested intracutaneously, before and after treatment, with a protein derived from beta-hemolytic streptococci.[15] All had negative tests before therapy. Nine patients who subsequently survived, and 3 others, who at autopsy showed no evidence of active infection, had a positive test after therapy. Two patients, however, whose tests remained negative after therapy did show actively infected valves at autopsy.

One patient, who relapsed three times before she was finally cured, showed a positive skin test shortly after each course of treatment. The test subsequently reverted to negative on three occasions, each time preceding bacteriologic and clinical relapse. After final recovery the skin test remained positive over a four-year period until death from congestive failure.

To some extent weight loss and the degree of anemia depended upon duration of infection before admission; a corollary of this finding was the absence of anemia in 25 per cent of the patients before the start of treatment. Although the erythrocyte sedimentation rate was elevated in most patients on admission, the rate did not always fall with successful treatment.

Treatment and Results

When this series was first begun in 1944, penicillin was scarce, and optimal doses were unknown. At that time, therapy consisted of 200,000 units of penicillin given intravenously for fourteen days. Duration of treatment was soon extended to three and then five weeks or longer, depending on the clinical response. At present, 2,000,000 units or more is given daily in divided doses intramuscularly every three hours, with the use of combined sodium and procaine penicillin in the latter weeks of therapy. Cure has resulted from as little as 200,000 units daily for two weeks or as much as 4,000,000 units daily for six weeks, but no one treatment schedule has been uniformly successful. Four patients with persistent fever and bacteremia received in stepwise fashion increased amounts of penicillin. Three of them responded satisfactorily within two to four days to the change in treatment. Despite changing therapeutic practices, a relatively stable year-to-year penicillin cure rate has been

Table 1. *Etiologic and Predisposing Factors in 40 Treated Episodes of Subacute Bacterial Endocarditis.*

Effect of Treatment	Average Age at Onset‡	Episodes in Male Patients	Episodes in Female Patients	Episodes in Patients with Predisposing Rheumatic Heart Disease	Episodes in Patients with Predisposing Congenital Heart Disease	Episodes in Patients with No Known Predisposing Heart Disease	Infections Following Major Dental Treatment Without Penicillin Prophylaxis
	yr.						
Cure*	36	13	15	23	3	2	10
No cure†.....	30	6	6	10	3	0	5
Totals		19	21	33	6	2	15

*28 episodes.
†12 episodes.
‡Average for entire group, 34 yr.
§Average for entire group, 3.6 mo.

Table 2. *Clinical Findings in 40 Episodes of Subacute Bacterial Endocarditis before Treatment.*

Type of Case	Symptoms					History of Murmur	Physical Signs				
	Infectious	Embolic*	Suggestive of Early Cardiac Insufficiency	Arthralgic	Major Embolic		Murmur on Admission	Fever on Admission	Fall in Temperature with Treatment	Pulse above 90	Petechiae
Episode later cured...	28	9	3	9	3	25	28	18	26	15	13
Episode not cured....	11	6	9	6	4	12	12	11	1	11	7
Totals	39	15	12	15	7	37	40	29	27	26	20

*Petechiae, etc.
†This group totals 36 because of deaths during early treatment or because data were not available.

observed, with an over-all result of 28 cures in 40 episodes, or 70 per cent (Fig. 1). That only the patients with the more refractory cases of subacute bacterial endocarditis were sent to the hospital in the last few years may explain the paradox of a stable annual cure rate in the face of increased treatment schedules.

Twenty-six of 28 cured patients showed a fall in temperature and pulse rate within forty-eight hours after the start of treatment,[10] and both temperature and pulse fell to normal within five to ten days. In contrast, 11 of 12 patients subsequently dying of the disease showed no fall in temperature with treatment.[4] Other clinical and laboratory evidences of healing were slower to appear. Encouraging signs, however, were clearing of the urinary sediment, disappearance of the anemia, return of the sedimentation rate to normal and disappearance of splenomegaly.

TABLE 1 (*Concluded*).

Effect of Treatment	Infections Due to Alpha-Hemolytic Streptococcus	Infections Due to *Staphylococcus Albus*	Infections Due to *Streptococcus Faecalis*	Infections Due to *Alcaligines Faecalis*	Infections Due to *Escherichia Coli*	Infections Due to *Gaffkya Tetragena*	Infections Due to Pneumococcus Type 15	Average Duration of Infections§
								mo.
Cure*	22	4	1	0	0	1	0	3
No cure†	11	0	0	1	1	0	1	4
Totals	33	4	1	1	1	1	1	

TABLE 2 (*Concluded*).

Type of Case	Physical Signs			Protein in Urine	Red Cells in Sediment	Casts in Sediment	Leukocytosis	Elevated Sedimentation Rate		Subnormal Hematocrit	
	Clubbing of Fingers	Splenomegaly	Congestive Failure					Before Treatment	After Treatment	Below 40 per cent	Below 30 per cent
Episode later cured...	8	15	3	12	11	7	6	21	17	20	5
Episode not cured....	6	10	10	9	9	8	6	11	7	10	6
Totals	14	25	13	21	20	15	12	32	24†	30	11

Drug-Resistant Organisms

Gram-negative bacilli were present along with the alpha-hemolytic streptococcus in 2 patients, neither of whom responded to available therapy, and both subsequently died. In this series no other organisms were found to be insensitive to penicillin in vitro.

Complications

In Table 3 are listed the important complications that occurred during the course of subacute bacterial endocarditis in the 38 patients of this study.

Cardiac Failure

Congestive failure occurred in 38 per cent of this group at some time. Failure developed in 13 during the course of the untreated disease, and despite therapy, 77 per cent of these patients subsequently died. Failure appearing for the first time in the immediate post-treatment period occurred in only 2 persons. The onset of failure in these 15 patients was not related to duration of infection before admission.

Findings at autopsy on patients dying with congestive failure in this disease indicated that the failure was due to new lesions of the myocardium as well as to valvular changes. In this small group of 13 patients who died* during or shortly after therapy, the presence of failure in 10 was associated with diffuse myocardial damage in 8. Marked valvular damage was not always associated with failure, and in some cases failure was present despite remarkably well healed valves. There were 2 examples

*Thirteen patients were autopsied during or immediately after treatment. One of these, who was considered cured, died of a myocardial infarction due to coronary arteriosclerosis.

of single lesions as the cause for failure: a patient with subacute bacterial endocarditis of the right ventricular endocardium alone had a diffuse myocarditis, and another with a normal myocardium had gross destruction of both aortic and pulmonic valves. Rheumatic myocarditis was seen in only 3 of the 13 autopsied cases. Failure was present

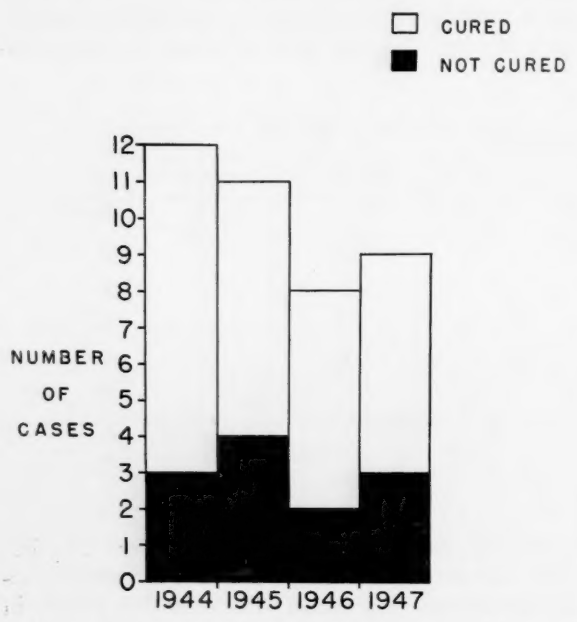

FIGURE 1. *Number of Treated Patients Cured per Year.*

in 2 of these, despite the absence of striking valvular damage.

Organisms highly susceptible to penicillin in vitro were found in the hearts of 8 of the 12 patients who died of the disease and in 7 of the 10 who died with congestive failure, although all had received two to four weeks of penicillin therapy.

Nephritis

Four patients (10 per cent) had definite evidence of renal lesions; 3 had focal embolic glomerulonephritis at autopsy, and the other is living. Three of the four had clinical signs of renal insufficiency. One patient died of combined uremia and congestive failure; another, in whom urinary signs of a renal lesion developed in the course of the infection, has had microscopic hematuria during the two years since that time. All 4 had had subacute bacterial endocarditis for over two months before therapy, and 3 showed a good bacteriologic response to treatment.

Embolic Complications

Lung. Four patients (10 per cent) had clinical or autopsy evidence of major pulmonary embolism. All died, 2 of the consequences of repeated embolism, and 2 of cardiac failure. All had right-sided lesions of the heart, 3 being subacute bacterial endocarditis, and the other an auricular mural thrombus.

Spleen. Splenic infarcts were commonly demonstrated both by clinical signs and by pathological examination. Only 1 patient had a serious complication therefrom: death resulted from rupture of an infarct, with massive hemoperitoneum, one hundred and twenty days after initial treatment of subacute bacterial endocarditis, during a clinical and bacteriologic relapse.

Central nervous system. Clinically noticeable cerebral embolization occurred in 4 cases (10 per cent). One patient died of repeated cortical infarcts and terminal hyperpyrexia. Two others suffered subarachnoid hemorrhages, but recovered satisfactorily. A fourth had several severe bilateral middle-cerebral-artery emboli, with residual hemiplegia.

TABLE 3. *Complications Occurring During the Course of Treated Subacute Bacterial Endocarditis.*

COMPLICATION	NO. OF CASES
Congestive heart failure	15
Nephritis	4
Major damage to central nervous system:	
Subarachnoid hemorrhage with recovery	2
Multiple cortical infarcts, with death	1
Bilateral midcerebral-artery emboli, with residual hemiplegia	1
Major pulmonary emboli from right-sided cardiac lesions	4
Splenic infarct, rupture and death	1

Peripheral. In 1 patient an ulnar-artery aneurysm developed prior to treatment. Another had multiple subcutaneous abscesses from which the alpha-hemolytic streptococcus was isolated.

COURSE AFTER TREATMENT

Of the 38 patients in this study, 27 remained bacteriologically cured for more than a year. Nine of these were followed for four to six years, 12 for two to four years, and 6 for one to two years. Seven patients of this group died. A twenty-eighth patient, who was considered cured, died of a myocardial infarction due to coronary arteriosclerosis two weeks after treatment. Vegetations were found to be healed at autopsy. This patient was the only 1 who died during the first year following cure of infection. Table 4 presents data on the 7 patients who died during the period of follow-up study. Four patients died of congestive failure, 2 of recurrent subacute bacterial endocarditis, and another of an unrelated late postoperative complication.

Although 7 of the patients who recovered had some cardiac, renal or neurologic disability due to the infection, only 1 was believed to have died from such a disability (Table 5). It is interesting that in 3 of the 5 patients who showed cardiac decom-

pensation in the period after treatment failure first developed during the course of infection.

Follow-up x-ray examinations of the heart were made in 16 of the patients who recovered.* Six showed an increase in heart size since the time of infection; 8 showed no change; and 2 actually were observed to decrease in size. Major increases in heart size were associated with congestive failure in only 3 cases.

Cardiac murmurs that were different from those heard during the infection were observed in 9 of the 27 patients at follow-up examination. Four of the murmurs showed a gradually increasing intensity dating from the time of the endocarditis, whereas the other 5 were considered unrelated and due to progression of the rheumatic heart disease.

None of the patients had anemia.† The sedimentation rate was elevated in 5 patients without known cause. Two patients, 1 with nephritis and the other with congestive failure, had abnormal urinary sediments; none had diminished renal function. In all but 1 case the streptococcus skin test was positive.

Discussion

Forty episodes in 38 proved cases of subacute bacterial endocarditis treated with penicillin have been considered in the data given above. Each patient received at least ten days of treatment and was followed for at least one year, unless he came to autopsy before that time.

Before the advent of effective treatment, the diagnosis was often made by the eventual development of obvious signs. Now, however, early diagnosis is of practical importance, and one must suspect bacterial endocarditis in some patients even in the absence of classic signs. On admission, fully a quarter of the patients did not show an anemia, a fever or abnormal urinary findings.

Congestive failure developing during the untreated infection was one of the most ominous prognostic signs. Seventy-seven per cent of the patients with failure died during the course of the disease. In general, a more rapidly developing clinical picture presaged a poor outcome. Once treatment was initiated, failure of the temperature and pulse to fall within two to four days on increasing amounts of penicillin, failure of clinical and laboratory signs to recede and, particularly, failure of the skin test for streptococcus to revert to positive indicated a grave prognosis, even though blood cultures were negative and the organism sensitive to penicillin in vitro. Age, sex, duration of infection, underlying disease and predisposing causes did not appear to influence the prognosis. The 2 patients with penicillin-resistant organisms, *A. faecalis* and *Esch. coli*, succumbed to the infection. In no other case in this series was any organism resistant in vitro to penicillin, and yet at autopsy two thirds of the patients who died showed actively infected valves. A similar finding has been reported by other observers.[11, 17]

The incidence of congestive failure was considerably less than before the penicillin era,[18, 19] but it was still present in 38 per cent of our patients at some time, and in 27 per cent of 511 cases collected from the literature.[2, 5, 8-11, 14, 19, 20] In most cases congestive failure was believed to be due to a combination of myocardial lesions and valvular destruction. As pointed out by others,[14, 18] neither the degree of valvulitis nor the presence of myocarditis has been consistently associated with the presence of cardiac failure. Our findings, although not conclusive, are compatible with this view, and support the concept that multiple factors

Table 4. *Relevant Data on the Patients Who Died during Period of Follow-Up Study.*

Patient	Age at Death	Underlying Heart Disease	Valvular Involvement	Cause of Death	Interval Since Infection
	yr.				yr.
E. G.	17	Rheumatic	Wall of right ventricle; mitral.	Recurrent subacute bacterial endocarditis, cardiac failure	1.4
D. C.	51	Rheumatic arteriosclerotic	Aortic (tricuspid)	Recurrent subacute bacterial endocarditis, with cardiac failure	1.25
B. E.	21	Congenital	Patent ductus arteriosus	Late postoperative pulmonary hemorrhage	1.25
V. P.	61	Rheumatic hypertensive	Aortic	Cardiac failure	1.5
G. McL.	32	Rheumatic	Aortic and mitral	Cardiac failure	4.5
M. S.	42	Rheumatic	Aortic and mitral	Cardiac failure	4.6
I. D.	57	Rheumatic	Mitral	Cardiac failure	5.8

Table 5. *Disabilities Present Since Cure of Subacute Bacterial Endocarditis.*

Disability	No. of Cases
Cardiac failure	5
Developing during infection	3
Developing after infection	2
Renal insufficiency	1
Permanent neurologic damage	1
Total	7

*Evaluation of changes in heart size by x-ray study were made by Dr. Ray Healey, formerly resident in radiology, Peter Bent Brigham Hospital.

†We are indebted to Miss G. Lanman, who performed the laboratory tests reported.

are concerned in the production of failure in this disease. The presence of active bacterial endocarditis in 7 patients who died with cardiac failure, despite penicillin therapy, and the peculiar downhill course, once congestive failure had developed, suggest that a major change in the immune and tissue response of the host had occurred, allowing for the persistence of an ordinarily penicillin-sensitive organism. It is suggested that the development or progression of congestive failure, as a reflection of diffuse myocardial and valvular damage in many patients, may serve as a clinical indicator of such an alteration in the immunologic response.

Other workers have found an incidence of rheumatic myocarditis in this disease varying from 0 to 63 per cent (Table 6). Aschoff bodies were observed in the myocardium of 3 of the 13 patients who died during or shortly after treatment. Although the number of cases of proved rheumatic carditis was small, carditis was probably significant in the production of progressive failure seen in 2 patients, in neither of whom were the valve lesions striking. Opinion is as varied on the relation of rheumatic carditis to the development of failure[14, 18] in this disease, as it is on the causal[21] or coincidental[22, 23] relation of active rheumatism to the development of endocarditis itself.

TABLE 6. *Incidence of Rheumatic Carditis in Subacute Bacterial Endocarditis and Its Relation to Cardiac Failure.*

AUTHOR	NO. OF AUTOPSIES	CASES OF RHEUMATIC CARDITIS	CASES OF CONGESTIVE FAILURE
Gorlin et al.	13	3	2
Buchbinder and Saphir[13]	40	15	3
Hildebrand and Priest[17]	9	0	—
Tumulty and Harvey[16]	9	3	3
Matthew and Gilchrist[14]	16	10	9
Totals	87	31	17

In the pre-penicillin era, clinical renal insufficiency was present in 25 to 35 per cent of patients with subacute bacterial endocarditis, and 80 per cent showed some form of nephritis at autopsy.[16, 24, 25] The remarkable decrease in the incidence of clinically evident nephritis since the advent of penicillin, as shown in this study, is supported by the small number of cases mentioned in the literature. Less than 10 per cent of 115 cases had renal impairment.[10, 14] The occurrence of constant urinary signs in over half the patients may be explained by high fever in some and by renal infarction in others.

Pulmonary emboli, although clinically not common, were observed only in patients who later died. Major cerebral emboli did not affect the prognosis in 3 out of the 4 patients who had them.

In this group, cures resulted from widely varying treatment schedules, suggesting that in the past too much emphasis has been placed on the exact number of units of penicillin given daily and the minutiae of injection intervals. It obtains in subacute bacterial endocarditis as in other infections[26-29] that widely varying therapeutic regimens providing repeated intermittent elevations of penicillin blood levels two to ten times above the sensitivity of the organism in vitro are satisfactory for cure. Our experience and that of other workers,[30, 31] in achieving some cures only by stepwise increases in penicillin dosage, and the prompt response to appropriate therapy observed in our patients suggest that the cardinal principle of treatment in this disease is to alter the dose or injection interval if the temperature does not fall within two to four days on a particular regimen. In this series only 2 patients survived who failed to respond within this short period to the final increase in daily dose of penicillin. Our over-all aim has been to continue treatment until clinical and laboratory signs of cure appear, whether it be a matter of weeks or months.

The results of treatment in this group are in accord with a cure rate of 72 per cent in 817 cases collected from the literature.[1, 3-14]

An effort has been made to evaluate the effect of successfully treated subacute bacterial endocarditis on the prognosis of the underlying heart disease. Of the 7 patients who died a year or more after treatment, the 2 with recurrent subacute bacterial endocarditis, analyzed above, and the patient who died of an unrelated cause have been excluded from further consideration. Evaluation of the individual patient was difficult because each was in the age group in which death from the underlying heart disease was common, regardless of the intercession of subacute bacterial endocarditis. In spite of this difficulty in interpretation, however, the data suggest that damage from subacute bacterial endocarditis could have been involved in the death of 3 of the 4 remaining patients, all of whom died in cardiac failure. Although it may be suspected that cured bacterial endocarditis shortened life expectancy in those 3 cases, this group constitutes only a small number of the 27 successfully treated patients. In 1 patient (V. P.) previously afflicted with cardiac failure, which became progressively more severe during an episode of endocarditis, damage from infection probably was related to death in failure one and a half years later. In the other 2 patients (M. S. and G. McL.) the duration of symptoms and age at death were compatible at least with the individual predicted life expectancy.[32-35]

A quarter of the patients who were successfully treated suffered one or another disability as a result of the infection. In the immediate period after treatment cardiac failure that had not been present during the infection developed in only 2 patients in this group.

Summary and Conclusions

Forty proved episodes of penicillin-treated subacute bacterial endocarditis, with autopsy or long term follow-up evaluation, are presented. Etiologic and predisposing factors in this study were in accord with classic concepts of the disease. Fever and anemia on admission were absent each in approximately 25 per cent of the patients.

Congestive failure developing early in the course, rapidly progressing symptoms and signs, unremitting fever despite four days of penicillin therapy for a sensitive organism and a streptococcus skin test remaining negative in spite of continued therapy all indicated a grave prognosis.

Congestive failure was frequently associated with diffuse myocardial lesions, as well as valvulitis, and in many cases an active penicillin-sensitive bacterial endocarditis was present despite weeks of therapy.

Nephritis and major embolic complications have decreased in incidence since the penicillin era.

Cure was effected in 70 per cent, with a relatively stable year-to-year cure rate. No one treatment schedule was successful despite the greater availability of penicillin more recently.

Follow-up study indicated that three fourths of the patients who survived the immediate post-treatment period suffered no demonstrable ill effects from the infection. The remaining patients had some functional disability or died prematurely of causes directly related to the bacterial endocarditis.

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OBSERVATIONS ON THE DEVELOPMENT OF RHEUMATIC FEVER AND GLOMERULONEPHRITIS IN CASES OF SCARLET FEVER TREATED WITH PENICILLIN*

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THE clinical course of scarlet fever and of pharyngitis due to the beta-hemolytic streptococcus has undergone remarkable change in the past few years as a result of the widespread use of penicillin. The duration of the fever, discomfort in the pharynx, leukocytosis, elevated sedimentation rate and persistence of the causative organisms in the respiratory tract have been so much reduced that the acute phase of the infection lasts no more than one to three days. Most striking has been the almost complete elimination of the suppurative complications such as otitis media, suppurative lymphadenitis, paronychiae, pneumonia and meningitis, and the ease of their management by chemotherapy in the uncommon cases in which they occur. Attention has been sharply focused, therefore, on the very important group of sequelae that do not appear to be the direct result of bacterial invasion but are produced by some as yet unknown mechanism; these are erythema multiforme, sterile gangrene, scleredema adultorum, late generalized lymphadenopathy and, most important, acute rheumatic fever and diffuse glomerulonephritis. It is with these pathologic states involving the heart and kidneys that this paper is concerned.

That rheumatic fever and glomerulonephritis are preceded in most cases by infection of the upper respiratory tract with the beta-hemolytic streptococcus is generally accepted by most students of the two diseases. Because of this close association it appears possible, on theoretical grounds, to eliminate either or both of these late streptococcal complications by early eradication of the causative organisms during the acute phase of infection. It was for this purpose that the investigations reported below were carried out; patients with scarlet fever were treated with penicillin, and the incidence of rheumatic fever and glomerulonephritis determined. In the cases in which these diseases occurred careful detailed investigations of the clinical and laboratory features were made.

In 1948 Weinstein, Bachrach and Boyer[1] first noted the occurrence of rheumatic fever and acute diffuse glomerulonephritis in patients with scarlet fever who had been treated with 120,000 units of penicillin parenterally per day for ten days. The present paper is an extension and completion of this study. Later in the same year, Massell, Dow and Jones[2] reported the use of orally administered penicillin in patients with rheumatic fever who were either carriers of or infected by the beta-hemolytic streptococcus; no recurrences of rheumatic fever were observed in the cases of clinical pharyngeal infection receiving the antibiotic. The authors pointed out, however, that the number of patients treated was small and that the study may have been carried out in a period when the prevalent strains of streptococci were not particularly "rheumatogenic." The most recent investigation of the influence of the procaine-penicillin treatment of acute streptococcal pharyngitis on the subsequent development of rheumatic fever is that of Denny and his associates,[3] who found definite rheumatic fever to be eight and five-tenths times more common in untreated controls than in those given the antibacterial agent; "possible rheumatic fever" occurred three times more often in untreated patients. These data and those of Massell and his co-workers[2] appear to be in disagreement with those reported by Weinstein, Bachrach and Boyer[1]; the possible reasons for these discrepant observations are discussed below.

The occurrence of glomerulonephritis as a late complication of scarlet fever has been known for many years; careful study reveals an incidence of about 1 or 2 per cent of this renal sequel in untreated streptococcal pharyngitis. The clinical picture is usually very variable; in some cases only the laboratory features of the disease such as hematuria, albuminuria and cylindruria are present, whereas others may show rarely the complete syndrome of urinary abnormalities, azotemia, hypertension, oliguria progressing to anuria, convulsions, uremia and death. Most cases lie between these two extremes. Many patients with scarlet fever, especially those with severe rashes, have albuminuria and hematuria early in the course of the illness; these are probably due to fever and the action of the erythrogenic toxin on the kidney and are not related to glomerulonephritis. This diagnosis can be made only if a "latent" period of at least two weeks between the onset of the acute streptococcal infection and the appearance of abnormal constituents in the urine, with or without clinical manifestations, is present. We are unaware of any studies of the influence of the penicillin treatment of acute streptococcal infection on the subsequent development of glomerulonephritis.

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Methods

Every patient with scarlet fever admitted to the Haynes Memorial Hospital was treated with penicillin if the duration of the rash was less than forty-eight hours and no antibacterial therapy had been given prior to admission. An attempt was made to grade the severity of the illness on the basis of the height of the fever, the extent and severity of the rash, the intensity of the pharyngitis and the presence of such toxic manifestations as headache, nausea, vomiting, abdominal pain and arthralgia. The exact criteria for this classification have been described in detail in a previous paper.[4]

Throat and nose cultures were made at the time of admission and daily thereafter by means of sterile cotton swabs, which were streaked on blood-heart infusion-tryptose-yeast agar and seeded at the same time into broth of the same composition. As many of the strains as could be were later typed for M nucleoprotein, and all were examined for sensitivity to penicillin. The results of the latter studies have already been reported by Hartman and Weinstein.[5] Complete physical examinations were carried out daily; all temperatures were taken rectally every four hours. White-cell counts were determined at least twice a week, urine examinations a minimum of three times a week unless glomerulonephritis supervened, when they were carried out daily, and erythrocyte sedimentation rates once a week during the entire period of residence in the hospital. Electrocardiograms were taken daily in the majority of cases or, when this was not possible, a minimum of three or four times a week in every case during the entire period of inpatient observation. The appearance of the rash and of the pharynx was noted daily. Serum was drawn once a week for determination of antistreptolysin, antistreptokinase and anti-M antibody levels.

Practically all the patients were kept in the hospital for a minimum period of three weeks, whereas those who manifested a frank complication or showed any abnormality in the course of the disease were detained for longer periods. The majority of the patients were studied for varying periods after leaving the hospital; in most cases a minimum of three months of follow-up study, with a visit every one or two weeks, was carried out; in the cases in which rheumatic fever or glomerulonephritis was thought to be present the period of observation after discharge from the hospital was six months or longer. At each follow-up visit a complete physical examination was performed, a detailed history obtained and a white-cell count, urine examination, sedimentation rate and electrocardiogram carried out. Serum was also drawn at each follow-up visit for various immunologic studies.

The penicillin given to all the patients was the crystalline G preparation. Two regimens of therapy were used; most patients received 15,000 units dissolved in physiologic saline solution every three hours for ten days; a smaller group was given 100,000 units of antibiotic (in a tablet containing calcium carbonate as buffer) orally every three hours for ten days. Blood levels were not determined.

Results

A total of 167 patients were included in this study; of these, 127 received penicillin by the intramuscular route; the others were given the antibiotic orally. One hundred and fifty were between the ages of two and fifteen years; 126 were less than ten years old. This represents a good sampling with respect to age since most were in the group in which the incidence of rheumatic fever and glomerulonephritis is highest after infection with the beta-hemolytic streptococcus.

Cases of Rheumatic Fever

Twelve patients (7.17 per cent) of the entire group with scarlet fever who received penicillin (2 orally and 10 intramuscularly) had laboratory or clinical manifestations, or both, highly suggestive of acute rheumatic fever. Beta-hemolytic streptococcus (Group A) was isolated in all cases.

Age

Four patients were between three and five years of age, and 7 were between six and sixteen; 1 was thirty-one years old.

Time of Penicillin Treatment in Relation to Onset of Sore Throat

One of the most important factors influencing the occurrence of rheumatic fever after the penicillin treatment of streptococcal infection may be the duration of the interval between the onset of clinical manifestations and the first exhibition of chemotherapy. In the group of patients reported by Denny and his co-workers[3] penicillin was given as soon as possible after the appearance of the symptoms of pharyngitis. In the present study sore throat was present in 93 (57.6 per cent) of the entire group for twenty-four hours or less before therapy was instituted, and in 120 (71.7 per cent) the interval was forty-eight hours or less. In the patients in whom rheumatic fever appeared, pharyngitis had been noted for one day or less in 7 (58.3 per cent), for two days in 4 (33.3 per cent) and for four days in 1. It is apparent, therefore, that about 72 per cent of the entire group and 91 per cent of those in whom rheumatic fever subsequently developed had had clinical streptococcal disease for forty-eight hours or less before treatment with penicillin was instituted.

Latent Period

All the patients in whom rheumatic fever later appeared had a so-called "latent period," the

average duration of which was nine and two-tenths days. This is somewhat shorter than that reported by Faulkner, Place and Ohler,[6] who noted, on the average, a lapse of twelve days between the first symptoms of pharyngitis and the appearance of electrocardiographic abnormalities.

Fever

Only 5 of the 12 patients showed an appreciable rise in temperature during the period when clinical and laboratory changes suggestive of acute rheumatic fever were most evident. It is striking, indeed, that in the other 7 cases there was complete lack of a febrile response at times when arthralgias were present, new murmurs were appearing and the electrocardiogram was showing progressive changes. In 1 child who had signs of aortic regurgitation (present on re-examination six months after onset) without any electrocardiographic abnormality the entire episode was completely afebrile.

Arthralgia

Subjective or objective involvement of the joints is one of the major criteria for the diagnosis of rheumatic fever. Our experience with first attacks of this disease in children in whom streptococcal pharyngitis was not treated with specific antibacterial agents has impressed us, however, that migrating polyarthritis is uncommon and that migratory or nonmigratory polyarthralgia or, frequently, monarthralgia of quite short duration is much more frequent. Thus, in the days before penicillin treatment, we observed a young patient with an afebrile monarthralgia of one wrist of twelve hours' duration in whom congestive heart failure developed four weeks later and who after three years had mitral stenosis. Little significance can be attached to joint pains in the acute phase of scarlet fever so far as rheumatic fever is concerned, since arthralgia is not uncommon early in streptococcal infections, especially if the disease is severe. The latent period assumes great importance here. In the group of cases reported in this paper a total of 30 patients had arthralgia; in 18 it occurred during the first six days after the onset of pharyngitis and had, therefore, no probable relation to rheumatic fever. In the other 12, the joint manifestations did not appear until at least nine days after the onset of sore throat. Only 4 of these were classified as having rheumatic fever since they were the only ones who had additional evidence of this disease; all showed electrocardiographic abnormalities, and 2 had persistent cardiac murmurs that had not been present during the first week of hospital observation.

Appearance of Murmurs

Four patients who had no abnormal heart sounds or only "functional" ones at the time of admission to the hospital later manifested what were interpreted as "organic" cardiac murmurs during the period of observation. In 2 cases arthralgia was present; in 3, in which persistent signs of mitral insufficiency appeared, there were also electrocardiographic changes. The fourth patient was treated with penicillin within twenty-four hours of the onset of streptococcal pharyngitis but still showed signs of aortic insufficiency, which persisted; he had no abnormal electrocardiographic findings at any time. In 1 of the cases in which a mitral systolic murmur was first noted in the hospital, clinical evidence of mitral stenosis was present nine months after the diagnosis of rheumatic fever was first made.

Electrocardiographic Findings

Since electrocardiography may be of value in the diagnosis of rheumatic fever, it is essential to define the changes that are to be considered significant. It is common practice in reporting mass surveys to list all findings such as premature beats, shifting pacemaker, auriculoventricular nodal rhythm or other wholly normal variations, with the implication that they indicate cardiac involvement. In the present study all such deviations from the usual were considered insignificant. A few other more unusual departures from the normal pattern were also disregarded, provided they were stable during the entire period of observation and were present at the time of initial hospitalization. One patient, eight years old, consistently showed prominent S waves in all leads, with increased duration of the QRS complex to 0.09 second. Another had an even more unusual pattern, with prominent Q waves in the standard limb leads and in Lead CF_4. Neither of these children showed other evidence of heart disease or rheumatic fever. In 2 cases intermittent coronary sinus rhythm was present, but no significance was attached to it. There appears to be little difference of opinion concerning the frequency and importance of the development of auriculoventricular block as a manifestation of rheumatic activity; it makes little practical difference whether the cause of the disturbance is local or vagal. The principles and rules adopted for the diagnosis of prolongation of the PR interval are of great importance. We have used the tables of Ashman and Hull[7] with liberal interpretation. PR intervals exceeding the predicted upper limit of normal for age and rate by only 0.01 second were considered normal, those from 0.01 to 0.02 second borderline, those over 0.02 second probably abnormal, and those of 0.04 second or longer as definitely pathologic. Certain qualifications, however, limit the value of these arbitrary standards. Intervals that are unvaryingly prolonged in serial records throughout the period of observation must be viewed dubiously; these may represent an occasional normal variation, or may be due to a congenital conduction defect or

to a residual scar from previous inflammatory processes. PR intervals showing noteworthy variation from day to day are much more reliable. In this connection it seems worth emphasizing that a PR interval that increases, even a little, with a rise in rate may be an important finding — for example, a prolongation of only 0.02 second with an increase of thirty beats per minute. Normally the PR interval shortens with increasing rate, whereas the reverse would be expected if a process tending to interfere with recovery of the conduction tissue was present. Change in the position of the pacemaker as a cause of such variation with alterations in the heart rate must be kept in mind, however. This was observed in 2 patients; the PR interval in both cases was about 0.13 second, with a cardiac rate of from 50 to 60 per minute, and 0.16 second or slightly longer when the pulse was 90 to 100. The form of the P waves, however, was quite different in the two records. Careful study of the contour of the P waves will therefore eliminate this type of error.

Eleven patients of the 167 studied (6.5 per cent) showed electrocardiographic abnormalities. Ten (90 per cent) had significantly increased auriculoventricular conduction time. The PR interval was longest, 0.22 second, in a seventeen-year-old patient; in 6 cases it was 0.20 second or more, and in the remaining 4 the maximum values were 0.19, 0.18, 0.18 and 0.19 second at the ages of eight, three, four and four years respectively. As emphasized above, variation in conduction rather than a single value was considered significant. For example, an eight-year-old child had a PR interval of 0.14 second at a heart rate of 94 six days after the onset of scarlet fever. On the thirteenth day the rate was 88 per minute, but the interval had increased to 0.19 second. The latter value is only 0.02 second more than the upper limit of normal and, so, is no more than borderline; the increase of 0.05 second without change in cardiac rate, however, is undoubtedly significant.

Prolongation of the QT interval is a reliable and nearly constant finding in the carditis of rheumatic fever. The same principles are involved in the evaluation of the significance of changes in this measurement as are concerned in the determination of the importance of alterations in the PR interval. With 1 exception, all the patients in this study who had prolonged PR intervals at one time or another also had elongation of the QT interval, but not always in the same record. In addition, 1 patient exhibited definite lengthening of the QT interval without any evidence of increase in auriculoventricular conduction. Prolongation of the QT interval was not extreme in any case, the maximum being 0.04 second more than the upper limit of normal (as pointed out in the Table of Ashman and Hull[7]). In 7 cases there was at least one record with a QT interval longer than the upper limit of normal, whereas in 3 the actual value never exceeded normal; in all, however, there were serial changes of as long as 0.06 second, at comparable heart rates. For example, a boy with a cardiac rate of 91 on the fifth day of illness showed a PR interval of 0.16 and a QT interval of 0.28 second; on the eighth day the rate was 91 and the PR interval was still 0.16 second, but the QT interval increased to 0.34 second — a rise of 0.06 second. The PR interval did not increase until the thirteenth day in this case.

Changes in the ST segment and the T waves were not encountered in this series of rheumatic subjects, although 2 patients with acute glomerulonephritis showed flattening or inversion of the T waves in Leads 1 and 2. During the acute stage of scarlet fever there was slight to moderate depression of the ST segment and lowering of T waves in many cases; this was attributed to the tachycardia and fever. These early changes differed in no way in patients whose course was uncomplicated and in those who later had evident rheumatic fever. They are entirely nonspecific and occur with any type of infection associated with rapid heart rate and fever. The unmistakable pattern of pericarditis did not occur in this series.

Because there has been considerable discussion and controversy concerning T-wave changes, and since their evaluation is a great deal more subjective than measurement of the PR or QT interval, a preliminary study was made of the ventricular gradient in a group of 41 patients with established rheumatic fever not included in this paper. It was hoped that such an approach to the problem would place the evaluation of T-wave changes on a more objective basis. This did not prove to be the case, for the direction and magnitude of the gradient showed no abnormalities. This is not to say that departures from normal may not be found in some cases, but the fact that they were not encountered in 41 cases of active rheumatic fever selected on the basis of the presence of prolonged PR intervals renders the method unsuitable for routine use. It is noteworthy, however, that none of the group in which the gradient was investigated showed what were considered to be significant T-wave changes empirically, although some T-wave alterations were present that might have been considered important by other observers.

Unfortunately, because of the magnitude of the study, it was impractical to take multiple precordial leads, only Lead CF_4 being used. It was impossible, therefore, to attribute significance to changes in the T wave in the chest lead when this was an isolated finding. Changes in the contour of the QRS complex from one record to another indicated clearly that the position of the electrode was not constant. Even when the QRS complex remained essentially unchanged it was not thought safe to attribute significance to T-wave changes,

inasmuch as the two components of the ventricular complex may vary independently with variations in placement of the electrode. There seems to be no doubt that study of the precordial T wave would have yielded helpful information if multiple chest leads had been employed.

Recurrence and Persistence of Streptococci

Four patients showed return of beta-hemolytic streptococci to the respiratory tract after having been free of them for varying periods. In no case did pharyngitis recur, however. In all cases the bacteriologic relapse occurred after penicillin therapy had been stopped, and in 3 it was noted after clinical and laboratory evidence of rheumatic fever was already present. The incidence of recurrence of positive cultures in patients with rheumatic fever was almost identical with that observed in the entire group of those with scarlet fever given penicillin — about 33 per cent. As pointed out in other papers[1, 8] this was due not to failure of the antibacterial therapy but to contamination of treated patients by association with persons with fresh, acute streptococcal infections or by contact with medical and nursing personnel who were temporary carriers of the streptococcus. The data obtained in this study do not indicate any relation between bacteriologic relapses or recurrent streptococcal pharyngitis and the development of rheumatic fever.

Erythrocyte Sedimentation Rate

In only 1 case was the erythrocyte sedimentation rate elevated at a time when rheumatic activity was thought to be present. In 8 others it remained entirely within normal limits, whereas in 3 it fell from abnormal to normal heights while electrocardiographic changes were still in progress. The possible explanation for these unusual findings is discussed below.

Serologic Studies

None of the cases studied developed any detectable precipitin for the nucleoprotein M of the serologic type of streptococcus with which they were infected. Only 4 patients had a rise in antistreptolysin titer during the period of illness and follow-up study, and only 2 showed an increase in antistreptokinase activity to levels above normal. In only 1 case was both the antistreptokinase and antistreptolysin content of the serum elevated.

Manifestations Suggestive but not Diagnostic of Rheumatic Fever

The following signs and symptoms suggestive but not diagnostic of rheumatic fever appeared in the patients with scarlet fever during the period of hospitalization: all followed a latent period of at least ten days; periumbilical pain of three to five days' duration occurred in 4; arthralgia involving more than one joint and continuing for at least two days without electrocardiographic changes at any time appeared in 4; and repeated epistaxes lasting a minimum of three days were present in 4. No new cases of rheumatic fever were detected after the usual three weeks of hospitalization. A number of patients, however, had clinical manifestations in the first month after discharge that raised the suspicion of the presence of the rheumatic state. Thus, 8 had monoarthralgia or polyarthralgia, 6 had recurrent epistaxes, and in 11 there were bouts of abdominal pain. No new murmurs appeared in any case, and repeated electrocardiograms were consistently within normal limits. The significance of these "minor" manifestations in the absence of any of the "major" ones after an established streptococcal infection is difficult to evaluate in terms of a specific diagnosis of rheumatic fever. Those experienced with this disease have been impressed, however, with the occasional case in which only "minor" signs and symptoms are present and in which there is evidence of rheumatic heart disease later in life. Because of the difficulty in establishing the diagnosis of rheumatic fever in the cases reported in this paper, they have not been considered as proved but have been classified as suspicions of rheumatic fever and will be followed, if possible, for a number of years to determine whether or not rheumatic heart disease develops.

It may seem to some that the criteria used for the diagnosis of rheumatic fever are open to question. We believe, however, that the data have been analyzed critically and that the disease has not been "overdiagnosed." The combination of a proved streptococcal pharyngitis, a latent period, joint pains and electrocardiographic changes provides a set of circumstances that to our mind constitutes the syndrome of acute rheumatic fever. There were 4 patients in this group who showed such manifestations, 2 of whom developed new cardiac murmurs; in addition, there were 2 others who subsequently had evidence of valvular disease. If only these 6 cases are considered as proved rheumatic fever, the incidence of this post-streptococcal sequel is still 3.6 per cent in this series; this is very little different from that reported in many years prior to the use of penicillin treatment in streptococcal pharyngitis.

Cases of Glomerulonephritis

Six patients (3.53 per cent) of the group with scarlet fever who were treated early in the acute phase of their infection with penicillin showed clinical or laboratory evidence, or both, of acute diffuse glomerulonephritis as a late complication.

Age

The patients ranged in age from three to thirty-six years; 2 were three, 2 were six, 1 was fifteen, and the last was thirty-six years of age.

Time of Penicillin Treatment in Relation to Onset of Sore Throat

In 4 cases penicillin was given within twenty-four hours of the first manifestations of streptococcal pharyngitis, and in 2 others treatment was not instituted until sore throat had been present for about forty-eight hours. Thus, two thirds of the patients who subsequently had glomerulonephritis were treated for the initiating streptococcal infection within twenty-four hours of the time when it first became clinically apparent.

Latent Period

Many persons with severe scarlet fever may show albuminuria, cylindruria and varying degrees of hematuria in the first week of the disease; these urinary abnormalities are undoubtedly due to the combined effects of fever and the action of the erythrogenic toxin on the renal glomerular capillary. It is very important, therefore, to insist on a "latent" period — during which there are no abnormal constituents in the urine — of at least ten to twelve days before the diagnosis of acute diffuse glomerulonephritis is considered seriously. With this as a criterion none of the patients in this study showed any manifestations suggesting an important renal complication until eighteen to twenty-five days after the onset of streptococcal pharyngitis.

Fever

Only 3 patients showed any febrile response during the period when manifestations of glomerulonephritis were most evident; in no case did the temperature rise over 102°F. by rectum. In the remaining 3 cases the entire course of the renal disease was characterized by the absence of fever.

Abnormalities in the Urine

The diagnosis of glomerulonephritis was not made in the absence of any of the characteristic urinary abnormalities. Thus, all the patients showed, after a "latent" period, varying degrees of albuminuria, cylindruria and hematuria. As is seen in this form of Bright's disease, the quantity of abnormal constituents in the urine varied from time to time. The shortest duration of the disease was four, and the longest twenty-eight days. No case of subacute or chronic nephritis was observed in this study.

Clinical Signs and Symptoms

Only 1 patient had clinical evidence of glomerulonephritis; this was a thirty-six-year-old man in whom moderate azotemia, acidosis, hypertension and oliguria, in addition to cylindruria, albuminuria and hematuria, developed. Nitrogen retention and decreased urinary output persisted for about two weeks, hypertension was present until the fourth week, and the urinary abnormalities disappeared about twenty-eight days after their first appearance. The relative absence of clinical evidence of renal disease in most of these patients re-emphasizes the need for frequent examinations of the urine in the third to the sixth week after the onset of a streptococcal pharyngitis. Glomerulonephritis characterized only by the presence of abnormal constituents in the urine has also been observed in cases of scarlet fever not treated with penicillin. Failure to examine the urine at frequent intervals for several weeks after an acute episode of streptococcosis will cause these relatively mild nephritides to be missed completely. It may be such incidents that account for the cases of chronic glomerulonephritis discovered first in adult life without a history of an acute attack of this form of Bright's disease.

Erythrocyte Sedimentation Rate

Three (50 per cent) of the patients who had glomerulonephritis revealed elevation of the erythrocyte sedimentation rate during the course of this complication. In the others the sedimentation rate remained normal in spite of the presence of cylindruria, hematuria and albuminuria.

Recurrence of Streptococci

In no case of nephritis was there evidence of a secondary streptococcal infection prior to the onset of renal disease. In 3 cases bacteriologic relapse was noted; the reasons for this phenomenon were discussed above. As in rheumatic fever, there appeared to be no relation between the recurrence of positive cultures in the nose or throat (or both) and the development of the renal complication. No case of persistence of streptococci in the respiratory tract during or after penicillin therapy was noted.

Serologic Studies

None of the patients in this group developed any precipitin in their serum against the M nucleoprotein of the serologic type of beta-hemolytic streptococcus isolated from the respiratory tract during the acute phase of scarlet fever. Not a single case of glomerulonephritis showed any rise in antistreptolysin or antistreptokinase titer; this is quite striking in view of the association of high levels of these antibodies with this form of Bright's disease that is often cited.

Discussion

The exact incidence of rheumatic fever in the civilian population after infection of the upper respiratory tract with the beta-hemolytic streptococcus is unknown because of lack of adequate reporting of both streptococcal disease and its sequelae.[9] In scarlet fever, in which it has been the practice in the past to hospitalize many of the pa-

tients, the rheumatic state has been found to occur in about 5 to 10 per cent of the cases, with some variation from one year to another. In military personnel[10] (World War II) in whom large epidemics of streptococcal pharyngitis have been carefully studied rheumatic fever has been present in from 2 to 14 per cent. The occurrence of "atypical" cases in which the clinical picture may be suggestive but not diagnostic contributes to the inaccuracy in estimating the number of cases of rheumatic fever following any outbreak of streptococcal disease. In studies carried out at the Haynes Memorial Hospital for several years, the incidence of rheumatic fever ranged between 5 and 7 per cent, and that of glomerulonephritis was about 1 per cent in over 2000 patients with scarlet fever who received no specific antibacterial therapy. The investigations reported in this paper suggest strongly that the early treatment of streptococcal pharyngitis with as effective an antibiotic agent as penicillin does not reduce appreciably the risk of either rheumatic fever or glomerulonephritis as "late" complications.

The investigations of Massell and his co-workers[2] and of Denny et al.[3] suggest that the occurrence of rheumatic fever is markedly reduced by treatment of the initiating streptococcal pharyngitis with penicillin. These studies and the one here reported by us are not completely comparable because of the lack of serial electrocardiographic determinations in the cases reported by Massell and Denny. Since, as pointed out above and discussed again below, many of the cases of rheumatic fever occurring in patients who have received penicillin treatment may be very mild and can be detected only by electrocardiographic studies, most of the cases of this disease may have been overlooked by the other investigators. Our group of patients and those of Denny et al. both received antibiotic therapy early in the course of the acute streptococcal infection. Furthermore, the speed of eradication of the streptococci from the respiratory tract is just as rapid when frequent injections of crystalline penicillin G are administered as when the depot type of antibiotic is given. One essential difference in this investigation and that of Denny and his co-workers was the difference in ages of the two groups of patients; ours were practically all children, whereas the others were primarily young adults.

The diagnosis of rheumatic fever is often very difficult to establish during the acute phase of the disease, and in many cases, observations extended over a period of years are necessary before evidence of rheumatic heart disease is available. About 10 to 15 per cent of cases may be free of cardiac involvement, — this is probably much more frequent in older adults, — and the presence of rheumatic fever is never established, particularly if the manifestations in the early stages have been atypical. Jones[11] has attempted to bring some order out of this diagnostic confusion by suggesting the use of certain "major" and "minor" criteria. The "major" manifestations include carditis — physical findings of cardiomegaly, significant cardiac murmurs, pericarditis or congestive failure and electrocardiographic changes, especially prolongation of auriculoventricular conduction time; arthralgia — of greatest significance if a patient is known to have had a streptococcal infection within two or three weeks; chorea; subcutaneous nodules; and recurrences of rheumatic fever. The "minor" criteria are fever, abdominal pain, precordial pain, rashes, particularly erythema marginatum, epistaxis, pulmonary findings, leukocytosis and elevated sedimentation rate. The presence of "any single major manifestation with at least two of the minor manifestations would seem to place the diagnosis on reasonably safe grounds." Jones[11] has stressed the importance of proved streptococcal disease in arriving at a diagnosis of rheumatic fever. Sokolow and Snell[12] commented on the significance of arthralgia and arthritis after a streptococcal infection in association with fever and elevated sedimentation rate in suggesting the presence of rheumatic fever in young adults. These investigators, Rosenberg[13] and Kimbro[14] noted, however, the frequency of monarticular involvement and the fact that joint manifestations may be minimal or absent.

There is little doubt that the use of the criteria of Jones[11] makes rheumatic fever more readily diagnosable in many cases. There are still many cases, however, in which only "minor" manifestations constitute the entire acute phase or in which the onset is so mild that the disease is completely overlooked. This is borne out by the well known clinical observation that about 50 per cent of patients with mitral stenosis can give no history of a preceding attack of rheumatic fever. This situation cannot be attributed to failure of physicians to make the diagnosis of the rheumatic state in cases in which typical attacks occur but must indicate that a large number of episodes of rheumatic fever are completely missed because they are so mild or so uncharacteristic that they do not attract the attention of the patient or his physician.

Although the diagnosis of rheumatic fever in most of the cases described above depended in great part on the demonstration of electrocardiographic abnormalities appearing after a "latent" period, a number of the patients had other criteria suggestive of this disease. The importance of changing electrocardiographic patterns in establishing the presence of rheumatic fever appears to be well established and is supported by many statements in the literature. The significance of cardiac involvement as the only manifestation of the rheumatic state has been stressed by Swift[9]: "All students of this disease recognize that a fair proportion of patients with rheumatic carditis have no

other outstanding symptom of rheumatic fever." Sokolow and Snell[12] have made the following comments:

> The diagnosis of carditis, the most important major manifestation, has depended largely on significant transient electrocardiographic changes, particularly partial auriculoventricular block and inverted T waves in Leads 1, 2 and 4, alone or in combination. Other objective evidences of carditis have been less frequently observed.

Other investigators have also emphasized this point: Sokolow[15] states that "The most frequent criterion of carditis in rheumatic fever in young adults is represented by abnormalities in the electrocardiogram." Taran[16] considers "The most sensitive criterion for rheumatic activity for the present seems to be a careful study of the cardiac events in the electrocardiogram." And Pardee[17] observes: "On the other hand, it is certainly true that there are many instances in which the electrocardiogram may give the only sign of rheumatic activity." Wickström[18] found that 86 per cent of patients with scarlet fever had "early or late" electrocardiographic abnormalities; this incidence, however, seems much too high and may be accounted for by overemphasis on minor electrocardiographic changes probably related to the fever and tachycardia present early in the course of the streptococcal infection. Six per cent of patients with scarlet fever who received only symptomatic treatment were found to have electrocardiographic abnormalities by Faulkner, Place and Ohler[6]; it is interesting that in the series reported by us the incidence was 7 per cent. In a careful investigation of the cardiac status in patients with scarlet fever who were given no specific therapy, Watson, Rothbard and Swift[19] found early or late electrocardiographic changes in 22 of 110 cases. Rantz and his co-workers[20, 21] have indicated that about 15 to 20 per cent of adults with scarlet fever show abnormal tracings consistent with those found in rheumatic fever; arthritis was not always present, but the laboratory evidence of carditis was definite and persisted for longer periods if the joints were involved. The authors commented on the fact that "the observed electrocardiographic abnormalities are not unique to the post-streptococcic state but are identical with those previously discovered during the course of acute rheumatic fever."

Since there is very little doubt that the patients reported above suffered from rheumatic fever or glomerulonephritis in spite of the penicillin treatment of the initial streptococcal infection it is quite striking that, with occasional exceptions, both diseases were much milder than those in patients treated "symptomatically" or with sulfonamides and, in many cases, would not have been suspected if frequent serial laboratory studies had not been carried out. Since one of the important differences between rheumatic fever and glomerulonephritis developing in penicillin-treated in contrast to untreated patients is the persistence of the beta-hemolytic streptococcus in the respiratory tract in those not receiving the antibiotic, it seems reasonable to believe that the mild character of these complications was due to the rapid and complete removal of the causative organisms early in the acute phase of the scarlet fever. This suggests the possibility that many of the cases of rheumatic fever and nephritis studied prior to the widespread use of penicillin in the treatment of streptococcal pharyngitis represented the combined effects of persistent streptococcal infection and the rheumatic or nephritic state. That this may be so is supported by results of the serologic studies carried out. The removal of the antigenic focus from the respiratory tract by penicillin was so rapid that little or no antibody response occurred. The development of rheumatic fever and glomerulonephritis without any rise in antistreptolysin titer is indeed striking and raises great doubt of the significance of this antibody in the pathogenesis or diagnosis of either of these conditions.

The occurrence of both rheumatic fever and glomerulonephritis in patients in whom the antigenic focus of streptococci in the respiratory tract was removed early and in whom no antibacterial or antitoxic immunity could be demonstrated may raise the question of the importance of an allergic reaction to the streptococcus or its products in the pathogenesis of these complications. Although the development of a state of hypersensitivity is not completely ruled out because the antibodies studied may be of no importance and the ones that may be of significance cannot at present be investigated, it is interesting to speculate whether these late post-streptococcal sequelae were the result of a direct effect of the beta-hemolytic streptococcus or some of its components or toxins on the collagenous tissues of susceptible patients. On the other hand, sensitization in certain persons may take place so rapidly that eradication of the bacteria even early in the acute phase of streptococcal infection comes too late to avoid the initiation of the mechanisms that are responsible for the production of either rheumatic fever or glomerulonephritis.

Since both rheumatic fever and glomerulonephritis may occur in patients in whom the initial streptococcal infection is adequately treated with penicillin and since both diseases may be so altered that they appear without striking clinical manifestations but are characterized mainly by laboratory abnormalities, the need for careful follow-up study of acute streptococcal disease after antibiotic therapy is stopped, even though there is no outward evidence of one of the post-streptococcal sequelae, is self-evident. The eventual outcome of the mild cases of rheumatic fever cannot be predicted accurately, but there is already evidence that in some signs highly suggestive of rheumatic damage to the valves may sub-

sequently develop; these patients will need to be followed for a number of years before a final decision regarding this point can be reached. The same situation obtains in the cases of glomerulonephritis that were observed. No case of subacute or chronic nephritis has yet been detected in patients in whom the disease developed after penicillin therapy had been given for the initiating streptococcal infection.

Conclusions

The treatment of scarlet fever with crystalline penicillin G does not prevent the development of rheumatic fever or glomerulonephritis as "late" sequelae.

Rheumatic fever occurred in about 7 per cent and glomerulonephritis in about 3 per cent of 167 patients with scarlet fever treated with penicillin.

Clinical manifestations of "late" streptococcal sequelae are usually mild or absent in patients who have received penicillin; the diagnosis of both rheumatic fever and glomerulonephritis depends heavily on frequently repeated laboratory studies such as electrocardiograms and urine examinations in these cases.

The usefulness of determinations of sedimentation rates and anitstreptolysin and anti-streptokinase titers in the diagnosis of rheumatic fever and glomerulonephritis is markedly reduced by prior penicillin therapy since most patients so treated do not show abnormalities in these laboratory findings.

Penicillin treatment of streptococcal pharyngitis does not eliminate the necessity of careful study of patients for at least four to six weeks after the onset of the infection by all the methods available for the detection of rheumatic fever and glomerulonephritis.

The rapid elimination of the beta-hemolytic streptococcus from the respiratory tract and the failure to develop detectable antibodies raises some question concerning the role of an allergic mechanism in the development of "late" post-streptococcal complications.

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INGUINAL ECTOPIA OF THE OVARY, TUBE AND UTERUS*

Report of a Case with Associated Genitourinary Anomalies

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TRUE inguinal ectopia of the ovary is a rare condition. It is always congenital, involves the fallopian tube, may involve the uterus and may be associated with other genitourinary anomalies.[1] The occurrence of a case of an inguinal ectopia of the ovary, tube and uterus associated with absence of the left kidney, an ectopic right kidney and congenital atresia of the vagina prompted this report. Mayer and Templeton[2] reviewed the literature of the world and reported 138 cases of true inguinal ectopia of the ovary. Only 10 of these involved the uterus, 3 had associated maldevelopments of the renal system, 14 had anomalies of the genital system, and only 2 had associated genitourinary anomalies as in the case reported below.

ETIOLOGY

The formation of a true inguinal ectopia is dependent on anomalous development of the genital tract. The müllerian duct and the mesonephric duct are intimately related in the first few months of fetal life. Toward the third month, the renal and genital systems are well separated, and the ovary has reached the false pelvis. The ovary passes into the true pelvic cavity by actual and relative descent because of the fixation of the gubernaculum of the ovary, the forerunner of the genitoovarian ligament, to the cornu of the uterus. The other end of the gubernaculum of the ovary reaches the base of the labium majus. The canal of Nuck, which extends into the labium majus at this point, usually becomes obliterated at the eighth month of fetal life. If, however, the canal remains open, shortening of the distal end of the gubernaculum or the change in the relative growth of the parts, together with failure of attachment of the proximal end of the gubernaculum, in time causes the ovary to be pulled into the canal of Nuck lying within the open inguinal canal. The tube follows the ovary into the canal, since the proximal portion of the müllerian duct is closely associated with the ovary in its development.

Although conclusions regarding the causative factors are based on known embryologic facts as well as anomalies found at operation, additional, less definitely proved factors undoubtedly play a role in their origin. As suggested by Donald[1] and others[2] a hormonal imbalance occurring at a critical stage in the development of the generative organs may underlie the anomalous results.

CASE REPORT

Mrs. H. H., a thirty-year-old woman, was admitted to the hospital on January 12, 1949, with a history of a mass in the left groin of 5 years' duration that had become increasingly painful during the past month. There had been no attacks of nausea or vomiting or any other systemic disturbance. The patient stated that she had never menstruated.

In April, 1943, she had been operated on for acute appendicitis. Physical examination at that time revealed the vagina to be a blind pouch 5 cm. in depth, and a pelvic mass on the right side palpable through the rectum was present in addition to the signs of acute appendicitis. At operation the right tube and ovary were normal, but the uterus and left tube and ovary were absent. Kidneys were not palpable in the normal position, but the tumor mass felt through the rectum was found to be a pelvic kidney approximately 7 cm. in diameter lying completely below the iliac vessels and behind the peritoneum. The appendix was gangrenous and was removed. The postoperative course was uneventful. Prior to discharge an intravenous pyelogram was obtained. The report was as follows:

> There is no evidence of stones. The right kidney is evidently down in the pelvis. There are no shadows of either kidney in the usual place. This patient may have ectopic kidneys, but only a part of the right kidney is visualized. So far as this examination is concerned there is only one kidney, and that undoubtedly is ectopic on the right side and is hydronephrotic.

In September, 1947, she was admitted to another hospital with the complaint of a painless soft mass in the left groin of 3 years' duration. Physical examination revealed an indirect left inguinal hernia. A Bassini type of herniorrhaphy was performed, but the report and findings of this operation could not be obtained. The patient stated that the mass in the left groin reappeared almost immediately after discharge and felt just the same as before the operation. However except for the presence of a mass, she had no discomfort and therefore did not seek any further advice until 1 month before admission to this hospital in January, 1949, because the mass had become painful.

Physical examination revealed a well developed, well nourished woman in no acute distress. The head and neck were normal, and the thyroid gland was not palpable. The heart was not enlarged, with no murmurs and with normal sinus rhythm. The lungs were clear and resonant throughout. The breasts were full and of normal consistence, and no palpable masses were present. The abdomen was soft and relaxed, with well healed right rectus and left inguinal scars. In the left inguinal region there was a soft, slightly tender, irreducible mass. There was normal distribution of pubic hair. Pelvic examination showed the external genitalia to be normal; the introitus was marital but nulliparous. The glands of Skene and Bartholin were not palpable, and the vagina was only 5 cm. deep, ending in a blind pouch. On bimanual examination no cervix or uterus was felt; the left adnexa could not be felt, and the right adnexa was palpable and normal. Examination of the rectum was negative.

The temperature, pulse and respirations were normal. The blood pressure was 110/70.

The urine was normal. The hemoglobin was 12 gm. per 100 cc., with negative serologic findings. The blood sugar, urea and urea nitrogen were all within normal limits.

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A left inguinal herniorrhaphy was performed, and a large hernial sac was located protruding through the left internal inguinal ring and extending through the canal of Nuck into the left labium majus. The sac, with its contents, was approximately 6 cm. in length and 3 cm. in width and was enveloped in a large pad of fat, with no evidence of scar tissue in that region. The sac was opened, and examination of the contents revealed a rudimentary uterus, a cystic ovary, a rudimentary fallopian tube and a piece of omentum. The omentum was replaced in the peritoneal cavity, and the hernial sac with its rudimentary contents excised at the internal inguinal ring. The uterus, ovary and tube were contiguous with the peritoneal sac. The neck of the hernial sac was closed with a silk pursestring suture at the internal inguinal ring, and a Bassini type of hernia repair performed with silk sutures throughout.

Microscopical examination of the hernial contents was reported as follows:

> The sections show pearly-white tissue of a firm consistence containing graafian follicles and cortical cysts. There is a perfect typical ovarian stroma. The block through the grayish mass is composed of bundles of smooth muscle. There is not an intact endometrium, but the texture and architecture are definitely those of uterine wall. The sections through the tissue that grossly looks like the tube show the wall definitely consistent with the wall of the tube even though intact endosalpinx cannot be demonstrated. The diagnosis is ectopia of the ovary, tube and uterus.

The postoperative course was uneventful, and the patient was discharged on the 10th day after operation. One month later the patient was cystoscoped. The urethra, as well as the bladder mucosa and trigone, was normal. The right ureteral orifice was normal in appearance and location, and a No. 6 ureteral catheter was passed easily for a distance of only 14 cm. No left ureteral orifice could be found. A phenolsulfonphthalein test of kidney function was performed intravenously, and the right ectopic kidney excreted 15 per cent of the dye in 15 minutes. Retrograde pyelogram showed the right kidney to be lying over the lower half of the sacrum on the right side and to have a congenital short ureter.

The complete diagnosis of the patient's condition, therefore, was ectopia of the left ovary, left tube and uterus, with absence of the left kidney, an ectopic right kidney and congenital atresia of the vagina.

Discussion

This case represents not only one of inguinal ectopia but also one with associated genitourinary anomalies. The fact that the patient reached the age of twenty-eight years without any symptoms is unusual, since most of the cases reported in the literature were observed in infants and children.

The contents of the sac contained a rudimentary uterus, a rudimentary tube, a cystic ovary and a portion of the omentum. The herniation of the omentum into the canal of Nuck was probably responsible for the patient's recent symptoms.

The most common complication of inguinal ectopia is torsion or strangulation of the tube or ovary or both. Changes frequently occur in the ovary, such as cystic or malignant degeneration. Occasional cases of salpingitis and ectopic tubal pregnancy have also been found. The only complication in the case reported above was the presence of the omentum.

The question may be raised concerning the authenticity of the diagnosis of true inguinal ectopia since a hernioplasty was followed by a recurrence a month later.

The details of the first hernioplasty are unobtainable since no pathological specimen was received for examination. The intraperitoneal operation performed in 1943 revealed the absence of the uterus, left tube and ovary in the peritoneal cavity. Therefore, it must be concluded that in 1943 the uterus, left tube and ovary were extra-abdominal, and that the first hernioplasty in 1947 was incomplete, with failure to remove the contents of the canal of Nuck, since as soon as the patient was ambulatory the inguinal mass reappeared. At the second operation for the hernia, exploration revealed the hernia to be an indirect one, and the contents of the canal of Nuck extended down to the labium majus and there was no evidence of scar tissue in the region of the sac.

Summary

A case of true ectopia of the left ovary, left tube and uterus, with absence of the left kidney, an ectopic right kidney and congenital atresia of the vagina, in a thirty-year-old woman is presented.

The etiology, incidence and complications of this condition are discussed.

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CLINICAL NOTE

BLACK TONGUE AS A RESULT OF ANTIBIOTIC THERAPY

Report of a Case

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THERE have been reports of black tongue occurring during therapy with the antibiotics. Harris† mentions it in his report after treatment with aureomycin, chloramphenicol (Chloromycetin) and penicillin. He believes that it is probably attributable to an actual deficiency of the components of the vitamin B complex, because of the destruction of the intestinal bacteria necessary for its synthesis or utilization.

I observed this condition (Fig. 1) in a patient taking aureomycin for a rapidly spreading pyoderma of the face. It appeared after the ingestion of 50 capsules (50 mg.) and disappeared without treatment ten days after the medication had been discontinued.

Figure 1. *Hairy Tongue Following the Ingestion of Aureomycin.*

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†Harris, H. J. Aureomycin and chloramphenicol in brucellosis: with special reference to side effects. *J. A. M. A.* **142**:161-165, 1950.

Correction. In the second part of the Medical Progress Report of Dr. George W. Thorn and his associates entitled "The Clinical Usefulness of ACTH and Cortisone," which appeared in the May 25 issue of the *Journal*, Table 2, on page 826, should have included a reference to the co-operation of B. J. Ferris, Jr., M.D., H. A. Kriete and J. L. Wittenberger, M.D., of the Harvard School of Public Health, on whose work the determination of changes in pulmonary physiology in a patient with allergic asthma on ACTH therapy was based. Also, the last sentence in the first paragraph on page 828 should be changed to read "It is of interest that the vitamin A level in the serum was significantly increased during ACTH therapy[104] — a finding of possible significance in view of the fact that a low vitamin A diet has been advocated in the treatment of psoriasis in the past."

MEDICAL PROGRESS

BODY-FLUID PHYSIOLOGY: THE ROLE OF POTASSIUM IN CLINICAL DISTURBANCES OF BODY WATER AND ELECTROLYTE (Concluded)*

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Hyperkaliemia causing symptoms is practically confined to patients with renal failure, advanced dehydration or shock. High serum potassium accompanied by high intracellular potassium occurs in adrenal insufficiency. The development is probably confined to advanced stages, when deficits of water are superimposed on deficiency of sodium.[62, 63] Although potassium is known to be unusually toxic to patients with adrenal insufficiency, the disturbances are not due simply to excess of potassium.[64] Heart failure and other disturbances caused chiefly by hyperkaliemia are seen in renal failure,[65-69] marked dehydration and shock.[52-54] Potassium intoxication can be produced by injudicious parenteral injections of potassium salts, but it is difficult if not impossible to produce potassium poisoning by oral administration except in patients with renal failure, shock or adrenal insufficiency.

The symptoms of hyperkaliemia are chiefly cardiac and are related to the elevation in concentration of potassium in plasma and not to the increase in intracellular potassium of the heart.[70, 71] A few patients with renal failure[18] have manifested a flaccid paralysis of the extremities but less striking paralysis of the neck, trunk and bladder. This weakness was relieved by measures that lowered the concentration of potassium in plasma. The following symptoms have been associated with elevation of the concentration of potassium in serum: listlessness and mental confusion; numbness and tingling of the extremities, with a sense of weakness and heaviness of the legs; cold, gray pallor; bradycardia and totally irregular rhythm; peripheral vascular collapse, poor heart sounds and low blood pressure; and ascending flaccid paralysis. The electrocardiographic changes accompanying high concentrations of potassium in serum are discussed below.

The diagnosis of hypokaliemia and deficiency of potassium is made by recognition of the disturbances known to lead to deficits of potassium, by the determination of the concentration of potassium in the serum and by the electrocardiogram. If the serum potassium is low, deficit of potassium in the extracellular fluids is established, and deficit within the cells is usually present. However, if there is dehydration and shock, deficiency of potassium in the cells may occur with normal or high concentrations in serum. For example, when infants with diarrhea or patients with diabetic acidosis are admitted to the hospital, normal or high serum potassium concentrations are usually found. After restoration of body water by administration of solutions containing sodium salts and glucose, the concentrations of potassium in serum may fall to quite low levels. As was indicated previously, there is unmistakable evidence of intracellular deficiency of potassium in most of these patients. The chief symptoms characteristic of potassium deficiency such as paralysis of skeletal muscles, electrocardiographic changes, intestinal distention and paralytic ileus are related to the low concentrations of potassium in the serum. However, the myocardial necrosis is probably caused by disturbances in the concentrations in the cells.

Hyperkaliemia is diagnosed from the symptoms, the analysis of the serum and the electrocardiogram.

The changes in the electrocardiogram with high and low concentrations of potassium may be described together since there are progressive changes in the electrocardiogram that correlate roughly with the concentration of potassium in serum.[9, 18, 28, 46] These alterations are represented diagrammatically in Figure 2. When the concentration of potassium in serum is below 3 millimols per liter, the following changes are likely to develop: slightly prolonged QT interval in relation to the PT interval; decreased height and inversion of the T waves; rounded, prolonged T waves; and possibly inversion of the P waves, extrasystoles and auriculoventricular block. The prolonged QT interval seems to depend on the prolongation of the T waves that may run into the P waves. These changes are not specific since they occur in other conditions. Their association with low serum potassium is evident when the changes disappear after the serum potassium concentration is restored to normal.

When the serum potassium concentration rises, the first change is alteration of the T wave, which becomes high and peaked. These changes begin to appear when the serum potassium concentration reaches 6.5 to 7.8 millimols per liter and are quite regularly present at concentrations of 8 millimols per liter and above. Heart block and irregular rhythm occur at 10 millimols per liter or slightly higher.

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The sequence of changes with increasing concentrations of potassium in serum is appearance of high, peaked T waves, increased duration of the PR interval leading to auricular standstill, biphasic curve with progressive delay in ventricular conduction and total arrhythmia leading to cardiac arrest.

The concentration of potassium in serum may decrease fairly rapidly owing to factors not involving the external balance. When this occurs, the decrease in serum concentration may be attributed to increase in extracellular volume, to increase in organic constituents of the cells that are accompanied by higher amounts of cellular potassium and to alterations in the activities and the structures of cells that lead to increase in cellular potassium.

In the first place, expansion of extracellular volume is most rapid and important when a decrease in extracellular water and electrolyte is restored by solutions containing sodium chloride and sodium bicarbonate. If extracellular volume is expanded from 0.15 to 0.25 liters per kilogram of body weight, the resulting concentration of potassium in serum will be six tenths of the initial concentration if the change is entirely dependent on the increase in extracellular fluids. This calculation suggests that a positive external balance of about 0.5 millimols of potassium per kilogram of body weight would be necessary to prevent the decrease in serum potassium concentration. Normally, the intracellular fluids limit the fluctuation in extracellular concentration of potassium because potassium enters the cells when extracellular concentrations rise or potassium leaves the cells when extracellular concentrations diminish. The state of intracellular potassium limits this reaction, particularly when there are deficits of potassium in the cells. Since intracellular volume is at least twice the volume of extracellular fluids, a decrease in extracellular potassium produces but a small change in intracellular concentration unless the transfer is confined to a small part of intracellular fluids. On the other hand a small increase in intracellular concentration will produce a significant decrease in extracellular concentration. There is evidence that adrenocortical steroids alter the distribution of water between intracellular and extracellular fluids. Desoxycorticosterone increases extracellular volumes and adrenocortical extracts increase intracellular volumes. Since these compounds also alter the ion transport the effect on the concentrations in extracellular fluids is modified by internal shifts of ions and renal excretion.[64, 72, 73]

Secondly, potassium enters the cells when certain structures are being formed. Since glycogen is deposited with about 0.36 millimols of potassium per gram of glycogen, a rough calculation of this factor can be made. By the use of Soskin's estimation of the increase in glycogen accompanying recovery from diabetic coma, about 1 to 1.5 millimols of potassium per kilogram of body weight, is transferred to the cells owing to glycogenesis. The role of glycogenesis in producing decrease in serum potassium is probably greater in diabetic coma than in other diseases because of the great depletion of glycogen stores and the rapid restoration of glycogen produced by administration of insulin and glucose. However, other disturbances should produce a similar reaction. In muscle, about 3 millimols of potassium is found for each gram of nitrogen. The over-all factor for the body may be somewhat smaller than the ratio in muscle. Although nitrogen can be stored, at least for short periods, without potassium, nitrogen storage eventually demands increase in intracellular potassium. There is some evidence that testosterone[74] produces accumulation of body protein that may lead to a low serum potassium concentration.

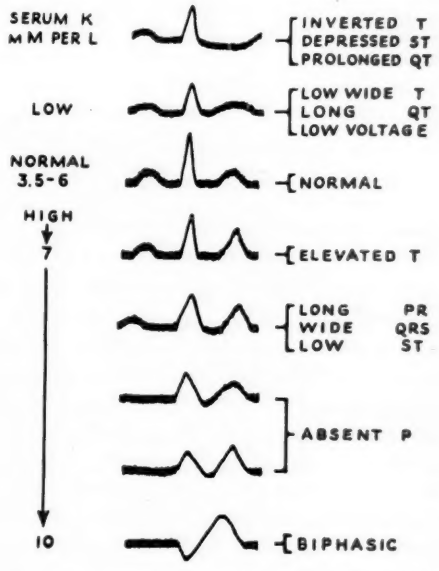

FIGURE 2. *Diagrams Representing the Electrocardiographic Changes Occurring with Changes in the Concentration of Potassium in Serum.*

Thirdly, there is evidence that anoxia and other disturbances in the metabolism of cells are accompanied by replacement of cellular potassium by sodium.[52-54] Reversal of this process must occur during recovery. This type of reaction must occur during recovery from shock. Administration of glucose may lead to the transfer of potassium to the cells owing to a change in the metabolism of the cells independent of deposition of glycogen.[75]

As indicated above, normal renal function protects the body from rises in serum concentration. However, with renal and circulatory failure, this mechanism fails.[76, 77] The source of the rise in serum concentration under these circumstances is the intake of potassium in food or as salts given as medicine and the release of potassium from the

cells. Catabolism of cellular structures releases potassium particularly when protein or glycogen is consumed. Anoxia, shock and failure of carbohydrate metabolism lead to release of potassium from the cells. The parenteral administration of potassium in inappropriate amounts and at too rapid a rate may produce potassium intoxication even in normal subjects. Potassium salts are particularly dangerous in patients with renal failure and adrenal deficiency.

The treatment of potassium deficiency should be considered one aspect of restoring tissue composition and function. Losses of water, sodium, chloride and phosphate are likely to accompany losses of potassium, or at least disturbances in the relative contents in the body of more than one of these constituents are likely to have developed. Therapy must also take into account other disturbances such as shock, circulatory failure and renal insufficiency. The problems of integrating potassium therapy into the therapy for other accompanying disorders is discussed elsewhere.[78]

Potassium chloride is usually the salt of choice since chloride and potassium deficiencies are likely to be associated with each other and because this salt is readily sterilized and may be given intravenously or subcutaneously as well as by mouth. Oral administration is relatively safe and, if possible, is the route of choice. The normal adult ingests about 4 gm. of potassium or the equivalent of about 8 gm. of potassium chloride per day. This amount can be given divided into two to four doses in twenty-four hours. The salt may be added to beverages or to food. Babies or children should be given corresponding amounts on basis of the relative caloric production rather than the weight. Howard[28] recommends a concentrated meat broth, an old-fashioned remedy, which has the advantage of containing large amounts of potassium together with other ions and cellular constituents.

The addition of potassium to various fluids given parenterally is rapidly coming into general use. This practice has proved to involve relatively little hazard and is life saving in appropriate cases. The addition of potassium is indicated not only to replace deficits but also to prevent deficits from developing. I originally used potassium in the treatment of dehydration in infantile diarrhea.[4] The solution contained 122 milliequiv. of sodium, 100 milliequiv. of chloride, 35 milliequiv. of potassium and 52 milliequiv. of lactate per liter (4 gm. of sodium chloride, 2.7 gm. of potassium chloride and 52 cc. of molar sodium lactate per liter). The solution was designed to give an amount of potassium that was safe in a volume of solution containing amounts of sodium and chloride that would replace the losses of these ions in severe deficit of extracellular electrolyte. The ratio of sodium to chloride is about the same as that of extracellular fluid, and 80 cc. per kilogram of body weight contains enough sodium and chloride to replace the deficits of these ions in severe depletion of extracellular electrolyte together with 2.8 milliequiv. of potassium. The solution may be injected subcutaneously but should be diluted one part to two or three parts of 5 or 10 per cent glucose if injected intravenously. The amount given in one day should seldom exceed 80 cc. per kilogram of body weight, and the total dose should be injected at a rate requiring four or more hours. When the serum concentration of potassium is likely to be high or when there is oliguria owing to circulatory failure, dehydration or shock, the administration of solutions containing potassium should be preceded by the injection of an appropriate mixture of solutions containing sodium chloride or sodium chloride and sodium lactate, together with glucose in water. Usually, the intravenous injection of about 20 cc. per kilogram of body weight is sufficient to restore the circulation and renal function so that it is safe to inject the solution containing potassium subcutaneously or intravenously. It is seldom necessary to delay the administration of solutions containing potassium for more than an hour. If recovery from symptoms leading to vomiting is rapid, potassium may be given orally at concentrations equivalent to the above solution diluted one part to two parts of glucose in water.

Butler and Talbot[79] have used a solution containing 30 milliequiv. of sodium, 22 milliequiv. of chloride, 15 milliequiv. of potassium and 3 milliequiv. of phosphate per liter of 5 or 10 per cent glucose. Except for the phosphate this solution is about the same as the one mentioned above when diluted with two parts glucose solution and should be given intravenously. The addition of phosphate is certainly indicated in diabetic acidosis and perhaps in other conditions.

Although more concentrated solutions of potassium than those described have been given intravenously without untoward results, solutions injected intravenously should probably not exceed 20 milliequiv. per liter in potassium concentration. Wallace and his associates[80] found that 3 milliequiv. of potassium per kilogram of body weight per day gave as great retentions as larger amounts up to 7 milliequiv. per kilogram per day. They emphasize that the repair of intracellular deficits is apparently a slow process. The patients with diarrhea studied have apparently required four to six days for restoration of intracellular deficits of potassium. Howard's[28] observations indicate that recovery from potassium deficit with alkalosis requires about six days. The amounts recommended above are apparently sufficient to prevent abnormally low serum concentrations of potassium. When deficits have occurred potassium administration should be continued for six days or until food can be taken in sufficient quantities to replace the deficits.

The solutions are appropriate for conditions associated with acidosis or for preventing deficits during maintenance of all fluid intake parenterally. For patients with alkalosis and deficit of potassium, a mixture of 6 gm. of sodium chloride and 2.7 gm. of potassium chloride is indicated. Such a solution may be injected with the same precautions by hypodermoclysis. If injected intravenously, it should be diluted one part to two or three parts of 5 or 10 per cent glucose in water. It may be desirable to add potassium chloride to intravenous fluids with relatively much less sodium chloride after the initial deficit of sodium has been replaced.

It is important to use potassium in its proper relation to other fluid therapy. When all fluids are given parenterally, the total requirement for water will be 100 to 150 cc. for each 100 calories metabolized when there are no unusual amounts of sweat or abnormal losses of water and electrolyte. The higher intakes are indicated when large volumes of urine are desirable or when they are necessary because of limitation in the ability of the kidneys to form a concentrated urine. If there are large deficits of water and electrolyte and large abnormal losses are occurring, the total intake should sometimes be as high as 300 cc. per 100 calories metabolized. The solutions should contain the appropriate amounts of the various ions that are necessary to restore the deficits and replace the continuing losses. In almost all disturbances the fluids per 100 calories metabolized should contain about 100 gm. of water without salt in the form of glucose solutions unless the serum is known to be markedly hypotonic. Rapoport and his associates[81] call attention to certain patients who have lost water and little or no electrolyte. These patients should receive glucose in water. It is not known whether they need potassium.

If there are no abnormal losses of water and electrolyte, the daily intake of electrolyte should be small; probably not over a fifth to a fourth of the total water intake should be made up with solutions containing salt at physiologic strength. It must be remembered that about half the water of physiologic saline solution is required to excrete the sodium chloride, and saline solutions are not appropriate means of giving water to cover the insensible losses and a large part of the urine water. When deficits of electrolyte are present, they usually require potassium as well as sodium and chloride for replacement. Continuing losses require more solutions containing electrolyte to cover the fluid requirements than when losses of electrolyte are minimal.

The administration of fluids during anuria and marked oliguria is a special problem that cannot be fully discussed in this paper.[82] However, it may be pointed out that the water requirement is decreased by the low urine volumes and that high intakes do not increase the urine volumes in oliguria due to intrinsic renal disease. Therapy should be planned to keep the water and electrolyte concentrations of extracellular fluids normal. The amount of potassium freed by tissue catabolism must be reduced as far as possible by the administration of glucose, and any food taken should be low in nitrogen and practically free of potassium. When urine formation starts, the intake of fluid is correspondingly increased. In some patients, salt will be wasted during recovery, and in others, it may be saved. Intake of electrolyte will therefore vary during the recovery from anuria and oliguria.

Coller et al.[83] have shown that for the first two or three days after operations, patients fail to show normal responses to certain renal loads that are frequently part of the postoperative care. The urine remains low in volume and contains little sodium even if glucose or saline solutions are given. If large amounts of saline solution are given, edema is likely to develop, and if large amounts of glucose solutions are given, the serum is likely to become hypotonic. For one to three days after operations, the intake of water and salt should take into account the low urine volumes and the low urine sodium. However, in shock there may be an obligatory expansion of extracellular fluids owing to the circulatory changes. Shock is best met by transfusions, especially transfusions planned to replace the losses occurring during operations. However, electrolyte may have to be given, especially if deficits of electrolyte play a role in the shock or low concentrations of electrolyte are present in the plasma. For uncomplicated cases requiring parenteral fluids, the total intake should be planned to cover the insensible loss (43 gm. per 100 calories metabolized) together with enough water to form low volumes of urine and provide some water for sweat.

At the site of burns and trauma, there is obligatory expansion of extracellular water and electrolyte together with varying amounts of plasma proteins. These constituents should be supplied in addition to the water necessary to cover expenditure of water and electrolyte.

Summary

The recent work on the relation of potassium to clinical medicine is reviewed. Changes in body water and electrolyte usually involve disturbances in body potassium as well as sodium, chloride and water. Acidosis may be explained by relative deficit of potassium or sodium or both. Alkalosis tends to produce deficit of potassium if renal adjustment is achieved. Deficit of potassium induces alkalosis if renal adjustment is achieved.

Loss of potassium is likely to occur when the intake is low, during parenteral administration with fluids containing no potassium, in diarrhea of various types, during postoperative gastric suction, after injection of desoxycorticosterone acetate, Cor-

tisone and ACTH, in some conditions associated with increased adrenocortical activity and perhaps in starvation.

The symptoms of deficiency of potassium and hyperkaliemia are briefly discussed.

Potassium therapy is discussed in relation to other fluid therapy.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

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CASE 36261

PRESENTATION OF CASE

A sixty-three-year-old woman was admitted to the hospital because of a suspicious lesion noted in the chest on x-ray examination.

The patient had been in excellent health until one month before entry, when she developed a pleuritic type of pain in the left subscapular region associated with a nonproductive cough. This subsided spontaneously after two weeks, and she felt quite well. X-ray examinations during this episode, however, showed a suspicious lesion in the left lower lung. Further x-ray studies of the gastrointestinal, genitourinary and skeletal systems were described as negative. Although she had noted mild dyspnea on exertion for several years, she had not experienced chest pain, cough or other respiratory symptoms. Systemic review was noninformative.

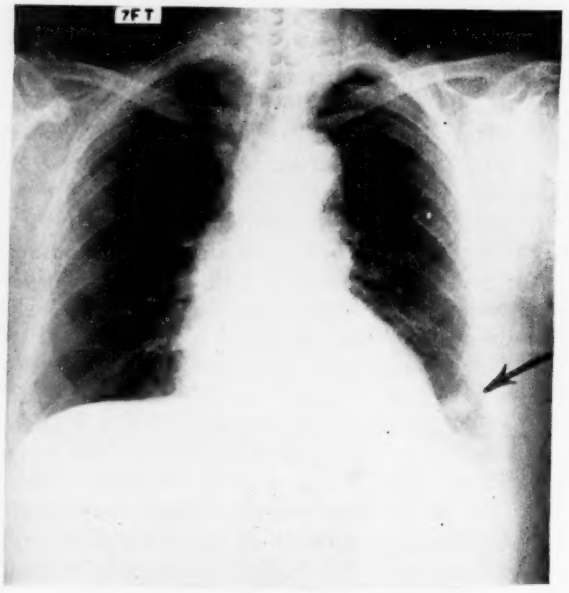

FIGURE 1.

The past history revealed that a left nephrectomy for a hypernephroma was performed twelve years before.

Physical examination showed a well nourished woman in no distress. The heart and lungs were clear. A well healed surgical scar was present in the left flank. The abdomen was nontender and free of masses. No organs were palpable.

The temperature was 98.0°F., the pulse 75, and the respirations 20. The blood pressure was 200 systolic, 110 diastolic.

The urine had a specific gravity of 1.020 and gave a + test for albumin, and the sediment contained rare erythrocytes and 10 leukocytes per high-power field. The hemoglobin was 13.4 gm., and the white-cell count 8600, with 50 per cent neutrophils, 47 per cent lymphocytes, 1 per cent monocytes and 2 per cent eosinophils. The total protein was 7.3 gm., and the nonprotein nitrogen 28 mg. per 100 cc. Cytologic examination of the sputum was negative for tumor cells. An electrocardiogram was considered within normal limits. A blood Hinton test was negative.

Examination of the x-ray films brought by the patient showed a rounded, 1.5-cm., homogeneous shadow in the left-lower-lung field (Fig. 1), apparently in the lingula close to the major fissure. The lung fields otherwise revealed no intrinsic diseases. The heart shadow was considerably enlarged in the region of the left ventricle, and the aorta was tortuous and calcified.

The patient remained symptom free following admission to the hospital. On the fifth hospital day an operation was performed.

Differential Diagnosis

Dr. Carroll C. Miller*: This case clearly calls for a discussion of the differential diagnosis of a discrete, rounded peripheral mass in the lung — a problem that is much in the minds and on the consciences of practitioners these days, especially those who are doing either medical or surgical chest work. This problem has been brought into much sharper focus recently as the result of the many chest-survey programs that are at present being conducted throughout the country. A not inconsequential number of such lung lesions have been discovered, demanding immediate decision about disposal. We have two approaches to consider in this particular case: one is a simple categorical listing of essentially asymptomatic lesions that can be seen in the lung fields by roentgenographic examination; and the other approach concerns the problem of whether or not there was metastasis to the lung from the hypernephroma that this patient had twelve years before.

Let me outline the various lesions encountered in the chest that may be entirely without symptoms and may have no relation to other conditions in the body. The first, the most likely and certainly the most serious lesion of this type is primary bronchogenic carcinoma. In the past few years we have been increasingly aware of the possible occurrence of small peripheral carcinomas in the lung, and this knowledge has brought us to the philosophy and the policy of assuming these lesions to be carcinoma until proved otherwise. As a corollary of this line of reasoning, exploration is carried out in a large majority of such cases unless there is some good reason to suppose that the lesion is not a carcinoma. There are a few points about this lesion as we see it on the x-ray film that speak somewhat against carcinoma. In the first place, carcinoma of the lung is less likely in women, although it is seen and therefore should not be discarded as a possibility. Again, the more frequent location for primary bronchogenic carcinoma is toward the hilus, but we have seen several similar cases in this hospital in the last year that have proved to be carcinoma; the lesion visualized by x-ray study was in the outer lung field, away from even the secondary bronchi. Usually the x-ray picture of a carcinoma is that of a round lesion, with perhaps indistinct, fuzzy margins, and clear evidence of atelectasis or infection distal to the lesion indicating obstruction of the bronchus from which the tumor arises. The margin of this lesion is sharp, and there is no surrounding reaction visible.

Tuberculoma is probably the next most common discrete lesion that we see in the lung, and there is usually no way of determining by physical examination or by other tests whether we are dealing with a tuberculoma or not. The chief factor that usually makes us decide that the lesion is a tuberculoma is its static condition. Whenever an x-ray film taken two or three years previously can be found, the same lesion can often be seen, and if it has not changed in size we can reasonably assume that it is a tuberculoma. However, a diagnosis of tuberculoma does not indicate that operation should not be performed because there is some danger of reactivation of the larger tuberculomas, rupture of the capsule and spread of tuberculous infection.

Adenoma of the bronchus usually occurs centrally although recently a sizable series of pulmonary adenomas occurring in the peripheral lung fields have been reported. Hamartoma of the lung also occurs more centrally as a rule. Any of the connective-tissue tumors that occur in the body in association with cartilage, bone or fibrous tissue may also be seen in the lung.

I think we can quickly dismiss any diagnosis of an active infectious or inflammatory process, the chief of which would be lung abscess or infarction. A lung abscess would make a person much sicker than this patient was, and x-ray examination should reveal more parenchymal involvement around the lesion. Certainly, this round, discrete lesion is not at all characteristic of a pulmonary infarct. So much for the various types of lung tumors that we may encounter.

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Regarding the possibility of metastatic renal-cell carcinoma, there was a long interval between the original operation and the discovery of the lesion in the lung. However, we are more and more willing to accept late metastasis, for in several different types of tumors elsewhere in the body we have encountered a single metastasis as much as ten or fifteen years after the original operation has been performed, an interval so long that we tend to forget about the original condition. It is my guess that this lesion was a metastasis from the hypernephroma. Since the first description of a resection and cure of a solitary metastasis from a hypernephroma was reported by Drs. Barney and Churchill,[1] of this hospital, in 1939, I think it would be interesting to read an excerpt from that paper:

> A careful search of the literature revealed no case identical with the one just reported. It is, however, well known that an isolated metastasis from a kidney tumor may occur both as an early manifestation of the disease and perhaps as the first and only evidence of it. It is of course well known that single or multiple metastases can occur as late as ten years after the recognition and removal of the kidney tumor.

This case was again reported in 1944 as a twelve-year cure. To the best of my knowledge, the patient is still alive.* Another discussion of metastatic hypernephroma was given in a paper by Linton, Barney and their associates[2] in 1946, in which they described metastasis of hypernephroma to the thyroid gland nine years after nephrectomy for renal-cell carcinoma. In addition in this case another renal-cell carcinoma was found in the remaining kidney at the time the thyroid lesion was discovered. The question was brought up at the time whether the metastasis to the thyroid gland might not have been from the second hypernephroma. However, in this paper 4 other cases were cited from the literature in which metastasis from hypernephroma had occurred thirteen, ten and eight years following removal of the original kidney lesion. Presumably, no other evidence of metastasis was demonstrated at that time. None was mentioned.

Therefore, I think the fact that renal-cell carcinomas are known to release solitary metastases that grow slowly may help us to make a diagnosis of metastasis from hypernephroma to the lung in this case. The episode that directed the attention to the lung apparently was one of involvement of the pleura by a lesion that was slowly expanding and gradually reached the point where it caused symptoms. The lesion was peripheral in the lung and probably lay directly beneath the pleura. The pulmonary and pleural changes secondary to the lesion probably accounted for the localized pain and the nonproductive cough. The other data are of no particular significance. The urinary findings were a + test for albumin and rare erythrocytes, in addition to white cells, in the sediment. We are not told whether or not this was a catheter specimen. This patient may have had another lesion in the remaining kidney, — although the pyelogram was read as negative, — but our problem is to decide whether the lesion in the lung came from the original kidney lesion or whether it was one of these other conditions. On the basis of probability alone, I believe the most likely diagnosis is metastatic hypernephroma, with a second less likely possibility of primary carcinoma of the lung.

FIGURE 2.

I had the opportunity to review the x-ray films before discussing the case. In this posteroanterior film and on the spot film there is a small rounded mass near the apex of the heart in the lingular distribution. Dr. McCort, would you make any other comments?

DR. JAMES J. MCCORT: The appearance and location of the lesion is accurately described in the protocol. On the lateral film it can be seen within the inferior lingular segment adjacent to the major fissure. In addition, a small amount of fluid is seen in the left costophrenic sinus.

DR. MILLER: That would be the result of the pleuritic reaction that the patient had a month previously.

*Subsequently corroborated by Dr. Barney in a personal communication.

Clinical Diagnosis

Metastatic hypernephroma of left lung.

Dr. Miller's Diagnosis

Metastatic hypernephroma to lung.

Anatomical Diagnosis

Metastatic renal-cell carcinoma to lung.

Pathological Discussion

Dr. David Freiman: At operation, the lingula of the left upper lobe was removed. A nodule could be felt deep within the parenchyma, and section revealed a yellow mass, 1 cm. in diameter, showing areas of cystic degeneration (Fig. 2). On microscopical section, this proved to be a metastatic renal-cell carcinoma with characteristic clear cells. We had the opportunity of examining sections from the kidney removed at the other hospital twelve years before admission. The appearance of the renal tumor is identical with that of the metastasis and histologic evidence of renal-vein invasion was already present at that time.

Dr. Miller: I might say that in several of the cases of metastasizing hypernephroma that have been reported, the discovery of a single lesion has immediately preceded the fairly rapid appearance of other metastases so that the prognosis in this particular patient, I believe, must be guarded.

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CASE 36262

Presentation of Case

A seventy-seven-year-old widow entered the hospital complaining of severe lower abdominal pain.

The patient reported that she had had a "weak stomach" all her life, particularly under emotional stress. Six years before admission she began to have constipation and lower abdominal pain. A barium-enema examination at that time showed diverticula of the large bowel. The constipation continued, alternating with occasional bouts of diarrhea productive of mucus but never of blood. The patient used milk of magnesia, suppositories and occasional enemas. There were occasional bouts of lower abdominal pain, but six months prior to entry, shortly after the death of her husband, these began to increase in severity and intensity, occurred at least once a day and lasted two or three hours. The pain was steady and hard, with occasional spasms of increased severity. It occurred at any hour of the day or night and often awakened the patient from sleep. It was associated with considerable gas and occasional frank distention and was described by the patient as feeling "like a worm crawling across the lower abdomen." There was some associated right-upper-quadrant pain, and shortly before admission the lower abdominal pain began to radiate through to the back, requiring Demerol for relief. Infrequent episodes of vomiting were associated with the pain, but none had occurred just prior to admission. Little relief was afforded by a low-residue diet, belladonna, phenobarbital or Seconal. In the six years before admission the patient had lost 25 pounds, but had gained 10 pounds in the six months prior to admission.

Physical examination revealed a well nourished, well developed woman in moderately severe distress who wept frequently. Both fundi showed arteriolar narrowing and tortuosity, with arteriovenous nicking. A Grade II systolic murmur was heard at the base of the heart. The abdomen was soft, and no masses or organs were felt. There was tenderness in the right costovertebral angle, at the right costal margin and in the right lower quadrant. Hyperactive peristalsis was clearly heard. There was minimal pretibial pitting edema on the left associated with superficial varicosities.

The temperature was 98°F., the pulse 84 and regular, and the respirations 18. The blood pressure was 180 systolic, 80 diastolic.

Examination of the blood disclosed a hemoglobin of 12.6 gm. per 100 cc. and a white-cell count of 8400, with a normal differential. The urine gave a + test for albumin, and the sediment contained 10 white cells per high-power field, some of them in clumps. Several stool examinations were guaiac negative. The nonprotein nitrogen was 24 mg., and the serum protein 6.6 gm. per 100 cc., and the prothrombin time 17 seconds (normal, 17 seconds). An electrocardiogram was within normal limits. A chest film showed pulmonary emphysema. On barium-enema examination the large bowel filled easily to the cecum, but the appendix and terminal ileum were not visualized. Multiple diverticula were seen in the sigmoid; however, there was no narrowing of any part of the colon, and the sigmoid was not fixed. Two gastrointestinal series showed a normal esophagus and a small diverticulum on the lesser curvature of the stomach, which showed active peristalsis and emptied promptly. In the first series of films an inconstantly dilated loop of ileum was visualized in the right lower quadrant. In the second series a dilated loop of ileum was again demonstrated, and just distal to it was a narrowed area, 2 cm. in length, with sharply defined margins (Fig. 1). There was no fixation of the terminal ileum and no evidence of obstruction.

The patient continued to have frequent severe attacks of lower abdominal pain, which were only partially controlled by atropine, Sodium Luminal and Demerol. The abdomen remained soft, and high-

pitched peristalsis was clearly audible, especially in the right lower quadrant. She continued to pass gas by rectum and had several bowel movements.

On the fourteenth hospital day an operation was performed.

Differential Diagnosis

Dr. Charles G. Mixter, Jr.*: I wonder if we could see the x-ray films first.

Dr. Stanley M. Wyman: The chest is not remarkable except for the prominence of the left ventricle of the heart and the tortuous calcified aorta. A single film from the barium-enema examination shows diverticula in the region of the sigmoid. The esophagus, stomach and duodenum are not remarkable except for the small diverticulum described. The important finding seems to be the unusually widened loop of ileum with some narrowing distally and a question of another area of narrowing more proximally (Fig. 1). This is seen on two films, and the dilatation is a little less prominent in the second. A spot film of these areas shows a widened ileum, and the adjacent segment of narrowed bowel seems to be somewhat conical and fusiform in contour.

Figure 1. *Barium-Enema Examination.*
The arrows indicate the definitely narrowed segment of ileum.

Dr. Mixter: This could not represent the "string sign" seen in regional enteritis?

Dr. Wyman: I think one should consider that as being a good possibility.

Dr. Mixter: Can you tell us anything about the mucosa in this segment?

Dr. Wyman: It is not too well shown. About all I can say is that I do not see normal mucosa, but I cannot exclude the possibility that some is present but not demonstrated.

Dr. Mixter: Where is the widened loop of ileum in relation to the ileocecal valve?

Dr. Wyman: It does not seem to be in the immediate region of the ileocecal valve.

Dr. Mixter: There was no fixation in that region?

Dr. Wyman: There was no apparent fixation.

Dr. Mixter: I concluded from the lack of their mention in the protocol that the pelvic and rectal examinations were negative and also that there was no history of a previous operation.

Dr. Helen B. Pittman: Yes; that is correct.

Dr. Mixter: No proctoscopic examination was done?

Dr. Pittman: No.

Dr. Mixter: It seems to me it would be fair to assume that this patient was suffering primarily from intra-abdominal disease and that therefore we can dismiss the findings not particularly applicable to the abdomen as signs that might be found in any patient of this age; among these are the cardiac, retinal, pelvic and vascular abnormalities.

We must next try to determine whether the symptoms of six years' duration were part and parcel of the present illness. This is a difficult decision because they could be readily explained on the basis of mild recurrent attacks of diverticulitis, diverticula having been demonstrated six years previously. However, at no time had there been any evidence either clinically or radiologically of acute diverticulitis. I believe we can tie the past symptoms in with the present illness. The last barium-enema examination demonstrated only diverticula without diverticulitis; there was apparently no spasm, narrowing or fixation in the area of the diverticula; and no other large-bowel lesion was demonstrable. I think it would be fair to turn our attention to the small bowel, where definite disease was shown by x-ray study. The x-ray report states that there was no evidence of obstruction, and yet on two examinations dilated loops of small bowel and also possibly two areas of narrowing were seen. Physical examination persistently showed high-pitched peristalsis. This, together with the "worm crawling across the lower abdomen," the distention and gaseousness, the occasional vomiting, and the alternating diarrhea and constipation point toward partial and probably intermittent obstruction. The location of the pain is consistent, as Jones† has pointed out, with disease of the lower ileum. He has further pointed out that pain in the back may be an outstanding symptom of gastrointestinal disease, although this could also be ex-

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†Jones, C. M. *Digestive Tract Pain.* 152 pp. New York: Macmillan Co., 1938.

plained on the basis of involvement of the root of the mesentery or retroperitoneal tissues by an inflammatory or malignant process.

I believe we can rule out an acute inflammatory process because of the relatively long history, the absence of fever and the normal white-cell count and differential. Certain chronic inflammatory lesions come to mind that must be considered. Regional enteritis would be extremely rare at this age, and the x-ray picture and history are hardly typical. However, as Dr. Wyman has pointed out, there are at least two areas that could be interpreted as being regional ileitis, but the patient was rather elderly for this type of disease unless the process was old and burned out. Certainly, the past history is not suggestive of regional ileitis. Abdominal angina could account for the symptoms, or an area of infarction might result in narrowing of the lumen of the bowel with partial obstruction. This diagnosis, however, is far from satisfactory. A chronic granulomatous lesion resulting from old perforation by a foreign body that had become walled off is a remote possibility. We have dismissed diverticulitis rather lightly, and it might be wise to say here that an inflammatory mass resulting from either diverticulitis or an old appendiceal abscess might give rise to involvement of a segment of ileum resulting in narrowing of the bowel. However, the radiologist states that there was no evidence of fixation, spasm or narrowing in the colon and that there was no area of fixation in the small bowel in the region of the narrowing, and in any event I should believe that evidence of inflammation should be more pronounced in either case. I believe we can dismiss such rarities as actinomycosis, tuberculosis and syphilis. Finally, obstruction due to congenital bands can probably be ruled out, for one would expect the patient to have evidence of these at an earlier age than seventy-seven.

A metastasis from an otherwise undisclosed primary lesion might well give us the picture of partial small-bowel obstruction without blood in the stools. The most likely source would be the colon, but there is no evidence for this and it would not account for the long history.

This leaves the large but relatively rare group of neoplastic conditions of the small bowel to be considered. These tumors, whether benign or malignant, usually manifest themselves first by symptoms of partial intermittent obstruction, either as a result of blockage of the lumen by their own bulk or by intussusception or constriction. They may produce symptoms almost identical to those of cholecystitis and peptic ulcer. Moreover, the patients frequently undergo multiple operations without the relief of symptoms because the true pathologic process is not discovered. Intussusception, more common in the benign group, occurs in approximately 30 per cent of the cases and gives rise to steady severe pain with an overlay of cramps. This might account for the type of pain that occurred in this patient.

Among the benign tumors one should mention hemangioma and myoma; these lesions almost always produce blood in the stools, which frequently is massive. This patient's stools were consistently guaiac negative. The x-ray picture in this patient is not consistent with fibroma, adenoma, papilloma or lipoma, which frequently cause symptoms of bleeding or obstruction, nor would it fit with cysts and aberrant pancreatic rests of the small bowel. Again, the average age is younger than that of the patient we are discussing. Neuromas and neuroblastomas are extremely rare lesions that must be mentioned but only in passing. They may be malignant and could fit the picture fairly well, since they may be slow growing, giving rise to symptoms of obstruction without ulceration.

Carcinomas of the small bowel, whether colloid, scirrhous, medullary or adenocarcinoma, are relatively rare, comprising only about 3 per cent of all carcinomas of the gastrointestinal tract. The x-ray picture and age of the patient under discussion are consistent with this diagnosis, and yet the sex of the patient and the lack of blood in the stool are against it. Moreover, one would be unable to explain the symptoms of six years' duration, and one would expect to find a rather pronounced anemia and a palpable mass. One would also expect at least some fixation of the area of involvement if the tumor was sufficiently old to produce obstruction and pain in the back resulting from mesenteric involvement.

Melanomas of the bowel do occur. Usually, they are metastatic and may occur years after the appearance of the primary lesion. These tumors are usually not ulcerated and therefore rarely bleed. They give rise to the same symptoms as other tumors of the small bowel but generally occur in the younger age group and are not likely to give rise to symptoms of six years' duration. Sarcoma and lymphoblastoma occur in the small bowel but usually grow outward from the lumen and hence rarely give rise to symptoms such as this patient had except as a result of a large bulky tumor, which would be readily palpable. These tumors, particularly lymphoblastoma, are moreover more prone to occur in the younger age group.

Finally, we come to a not uncommon condition in the terminal ileum that I believe best fits the picture. The average age for the patients with carcinoids or argentaffinomas in areas other than the appendix is about sixty-five. Aside from the appendix, the most frequent site is the ileum. They may go on asymptomatically for years as benign lesions, or give rise to only indefinite intermittent symptoms. Later, if they become malignant and metastasize to the regional lymph nodes, they give rise as a rule to progressive symptoms of partial intermittent obstruction. This process is often a slow one, for they are usually of a low grade of

malignancy. There is usually no ulceration of the mucosa and hence no blood in the stools. Anemia is rare. The x-ray picture is typically that of a localized constriction of the bowel consistent with what we have here. Since seeing the x-ray films, although that second bowel constriction does not preclude the possibility of carcinoid, I think it makes it a little less likely. Moreover, by suggesting metastatic involvement of the root of the mesentery and possibly also of the retroperitoneal tissues, we can explain the steady component of the pain and the pain in the back without postulating occasional episodes of intussusception for which we have little evidence. Intussusception caused by carcinoma of the bowel is rare.

I am frankly unable to account for the loss of 25 pounds in six years and then the gain of 10 pounds in the past six months during the more severe period of her illness. One remote possibility is that weight loss was a result of the intrinsic bowel lesion and that the recent gain was produced by the accumulation of fluid resulting from mild congestive heart failure. Again, we note that the patient was well developed at the time of entry, and she may previously have been somewhat obese and may have been put on a diet because of the hypertension.

We must still account for the right-costovertebral-angle and subcostal tenderness as well as the urinary findings of 10 white cells per high-power field. This could have been the result of partial ureteral obstruction from metastatic or inflammatory tissue and is the best explanation I can make.

In conclusion, my diagnosis is that of a tumor of the small bowel, probably primary and most likely a carcinoid; less likely possibilities are adenoma with malignant degeneration or fibroma. In addition, she apparently had diverticulosis, arteriosclerosis, hypertension, hypertensive heart disease and varicose veins.

Dr. Pittman: I did not get on the track of the small bowel for about a week or ten days. The patient had diverticulosis, and the story was that of partial intermittent obstruction that we were inclined to attribute to spasm, irritation and grief because the onset of the symptoms coincided with the death of her husband following which she went to live with a son and his children. It was only after diet and medication were given without relief that we began to look for something higher up in the small bowel and had these x-ray films taken. It was then we asked Dr. Allen to explore the patient.

Dr. Arthur W. Allen: I think Dr. Mixter is to be congratulated on the thoroughness with which he has discussed this case. We reasoned much as he did that regional ileitis was unlikely because of the age. We believed that the patient did have a tumor of the terminal ileum and we put down in the record that it probably was a lymphosarcoma. Before the patient was explored however, we made carcinoid our first choice. We thought that carcinoid would fit the x-ray picture and the history better than lymphosarcoma. We believed that carcinoma was less likely in this region but had to be considered, and we had considered tuberculosis a more likely possibility than Dr. Mixter did in his discussion. The interesting feature about it was that we could not make a diagnosis after we saw the lesion. After resection of the terminal ileum, the right colon with all the lymph nodes and the mesentery, Dr. Castleman looked at the specimen and quite frankly could not make a diagnosis either so that now, Dr. Mallory, you can tell us what it was.

Clinical Diagnosis

Carcinoid of small bowel.

Dr. Mixter's Diagnosis

Carcinoid of small bowel.

Anatomical Diagnosis

Regional ileitis.

Pathological Discussion

Dr. Tracy B. Mallory: The specimen that we received consisted of terminal ileum, cecum and a small part of the ascending colon. The most noticeable lesion was in the ileum, which was markedly thickened and constricted and showed an irregularly ulcerated mucous membrane. The microscopical sections of that were entirely characteristic of a regional ileitis in spite of the patient's age. The cecum, which I gather felt thick and abnormal at the time of operation, did not show any involvement with the ulcerative process but did show an abnormal pad of fat tissue in the submucosa that undoubtedly made the bowel wall feel thickened and abnormal. I think that was perhaps a congenital abnormality. The lymph nodes in the mesentery were considerably enlarged but showed nothing but an inflammatory hyperplasia. Naturally, the possibility of tuberculosis was very seriously considered, but nothing was found in either the bowel or the lymph nodes that would justify such a diagnosis.

Dr. Bernard M. Jacobson: I think I might have given a little more weight than Dr. Mixter did to lymphosarcoma, since it can occur in the later decades.

Dr. Mallory: We have seen lymphomatous involvement of the small bowel in elderly people, although of the tumors, carcinoid is by all means the most common.

Dr. Pittman: When Dr. Allen resected this he said: "Here is our carcinoid."

Dr. Allen: Yes; it looked quite like carcinoid on gross examination. The reason I removed the right colon was that I wanted to get above the lymph nodes, and we therefore had to include the blood supply to the right colon.

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PREVENTION OF RHEUMATIC FEVER AND ACUTE NEPHRITIS BY EARLY PENICILLIN TREATMENT OF HEMOLYTIC-STREPTOCOCCUS INFECTIONS

A recent study conducted at Fort Warren, Wyoming,[1] has brought forth evidence that rheumatic fever can be prevented by treatment of acute exudative pharyngitis with penicillin. In this study, a total of 798 patients whose Air Force serial numbers ended in even digits received penicillin treatment, and 804 patients whose serial numbers ended with odd digits comprised the control group, receiving no specific treatment. All patients admitted with exudative pharyngitis were included in the study, and 80 per cent in each group yielded positive cultures for Group A beta-hemolytic streptococci. Treatment with penicillin was begun within sixty hours of the onset of symptoms in 88 per cent.

Only 2 of the penicillin-treated patients subsequently developed rheumatic fever, whereas this late complication appeared in 17 of the control patients, and in each case the complication was recognized between the tenth and the thirty-fifth day after the onset of the pharyngitis. "Probable rheumatic fever" was diagnosed in 2 additional patients in the first group and in 6 additional control patients. Rigid criteria, based on a modification of those suggested by Jones,[2] were used in establishing the diagnosis in these cases.

Elsewhere in this issue of the *Journal*, in a report from the Haynes Memorial, Massachusetts Memorial Hospitals, Weinstein et al. reach the conclusion that the incidence of rheumatic fever and of glomerulonephritis is not reduced in cases of scarlet fever by prompt treatment with adequate doses of penicillin. This report is based on 167 patients, all of them treated with penicillin — and in about three fourths of them the first dose was given within forty-eight hours of the onset of symptoms. Rheumatic fever developed in 12 patients, or 7.2 per cent, after an average latent period of nine and six-tenths days, and evidence of nephritis was recognized in 6, or 3.6 per cent, of the entire group after a latent period of eighteen to twenty-five days from the onset of symptoms. The diagnosis of these complications was based on the demonstration of changes in the clinical and laboratory findings that were considered to be diagnostic in the individual cases and depended on careful and prolonged observation of clinical signs and symptoms and on serial laboratory tests, including electrocardiograms, made at frequent intervals.

Divergent conclusions such as those reached in these two reports have also been arrived at from several earlier studies. Thus, other workers in Army units,[3] on the basis of studies of the effects of sulfadiazine and penicillin, concluded that "penicillin did not appear to prevent the subsequent development of acute rheumatic fever in patients having nasopharyngitis, tonsillitis and scarlet fever due to group A hemolytic streptococci." Massell, Dow and Jones,[4] on the other hand, observed no recurrences of rheumatic fever among 10 patients with clinical and 5 with subclinical hemolytic-streptococcus infections acquired during conva-

lescence from rheumatic fever and promptly treated with penicillin. This observation is particularly significant in spite of the small number of patients involved because it is the general experience that recurrences of rheumatic fever follow hemolytic-streptococcus infections in about 50 per cent of the cases. Regarding nephritis, it is worth noting that Jersild[5] encountered not a single case among 2000 patients with scarlet fever following treatment with penicillin.

In spite of the clear contradictions in the conclusions drawn by the various workers about the late complications of hemolytic-streptococcus infections after penicillin therapy, the data presented in each of these studies are in remarkably close agreement in many other important respects. These all concern the effect on the streptococcal infection itself. In the first place, all the studies have shown that *adequate* treatment with penicillin results in eradication of Group A hemolytic streptococci from all but a very small proportion of the cases. This has been accomplished only by continuous therapy for seven to ten days and entailed the administration either of several doses each day intramuscularly or by mouth or the intramuscular injection of slowly absorbed preparations of procaine penicillin at intervals of two to four days. Secondly, such treatment produces a very marked drop in the incidence of the early suppurative complications due to hemolytic streptococci and almost completely eliminates such complications if the penicillin treatment is begun early. Finally, all observers have demonstrated significantly lower antibody responses, as judged by serial determinations of antistreptolysin O titers, in patients who are treated with penicillin early and adequately, as compared with those treated with sulfadiazine or those receiving no specific treatment.

There were considerable differences in the methods of administration of penicillin and in many other aspects of the various studies. However, most of these differences probably do not adequately explain the contradictory conclusions about the late complications except so far as the duration of effective, continuous penicillin therapy is concerned. In this respect there appears to be general agreement that prolonged maintenance of therapy is essential.

On the other hand, the basis for the diagnosis of rheumatic fever and the details of the data that were collected in order to arrive at this diagnosis have varied significantly. These alone may be largely responsible for the divergent deductions made by the different workers, particularly those at Fort Warren and at the Haynes Memorial. With respect to these two studies it is important to emphasize that the former included a carefully controlled and parallel series of untreated cases that offered a reliable basis for comparison, whereas all the patients in the latter series received penicillin. Moreover, the Air Force study was carried out entirely in young adults with "exudative pharyngitis," whereas the patients studied at the Haynes Memorial were predominantly children and all had scarlet fever and hence probably represented a much more severe type of infection.

It is of added interest to note that some of the cases of rheumatic fever and glomerulonephritis reported by Weinstein and his co-workers at the Haynes Memorial could easily have been missed, according to the authors themselves, were it not for the frequent, careful and prolonged clinical observations and the serial electrocardiographic tracings, urinalyses and other laboratory findings upon which the diagnoses were based. Thus, fever, objective changes in the joints and elevated sedimentation rates were absent in most of the patients who were considered to have rheumatic fever at the time when this diagnosis was made. Although the data from Fort Warren are not presented in complete and final form, it appears unlikely from the published report that the large number of patients dealt with permitted the accumulation of similar numbers of observations in the individual patients. The data obtained, however, were comparable to those collected by most other groups of workers in recent years.

It would, of course, be of considerable interest to know the incidence of late complications in a group of parallel untreated cases simultaneously studied in the same manner at the Haynes Memorial. It would also have been quite illuminating had the Fort Warren cases been studied in exactly the same

way and had the incidence of complications there been based on the same criteria as those used by Weinstein and his co-workers. One might safely hazard a guess that untreated control cases of scarlet fever at the Haynes Memorial would have had a much higher incidence of late complications than was actually observed there under early penicillin treatment. By the same token, were the criteria used at the Haynes Memorial applied to data similarly accumulated at Fort Warren, there probably would have been a greater incidence of late complications, but this incidence would have been much lower than that among the corresponding treated and control cases at the Haynes Memorial.

The assumption that rheumatic fever was not prevented in many of the patients whose scarlet fever was treated with penicillin at the Haynes Memorial is not necessarily valid, and the same reservation may also be made of nephritis. The fact that the numerical incidence of late complications in that series was similar to the incidence reported by many others in untreated cases of scarlet fever cannot be given undue weight in view of what has been said about the manner in which the diagnoses were made. It can only be stated, therefore, that the incidence of rheumatic fever and of glomerulonephritis is still significantly high in patients with scarlet fever who are treated with penicillin, provided that the criteria used for the diagnosis of these complications are those employed by Weinstein et al. and that the essential data are obtained in the same manner.

In the Fort Warren study there was a direct and statistically valid comparison of two similar groups of cases of streptococcal infections, which varied only in that penicillin was given to one of the groups. There was a highly significant reduction in incidence of rheumatic fever ascribable to penicillin treatment of the streptococcal disease. The criteria for diagnosis were essentially those generally used, and the same criteria were applied to both penicillin-treated and control cases. It seems reasonable to suppose that, if other criteria had been used, a similar difference in incidence of rheumatic fever among penicillin-treated and control cases would have been observed although the numbers of patients with this complication would have been quite different.

The findings of the workers at the Haynes Memorial also suggest that rheumatic fever and glomerulonephritis may appear in a highly modified and attenuated form if the antecedent streptococcal infection is treated early and adequately with penicillin. They have also shown that what they quite justifiably call rheumatic fever and nephritis can be recognized by proper and continuous attention to details. The ultimate fate of the rheumatic and renal lesions in these patients will be the determining factor in the estimation of their significance. If prolonged follow-up study reveals no progression of cardiac or renal lesions, it may be important to avoid making these diagnoses and, instead, merely to consider the findings as incidental and interesting complications of the original infection. Such serious labels, with their inevitable implications, are best avoided unless they represent definitive diagnoses.

This controversy brings into focus again one of the most important medical problems that require solution — namely, the establishment of criteria for the diagnosis of rheumatic fever that are valid, reliable and workable and are related to the subsequent development of permanent and serious disease.[2, 6, 7] The significance of attaching a diagnosis of rheumatic fever to a patient can hardly be minimized. It usually entails an enforced and prolonged rest, with all its economic implications. The psychologic impact on both patient and family may completely alter their activities and their social outlook. This diagnosis alone has a direct effect on the availability of a person for military service and when made in a member of the armed forces entails a sizable financial outlay on the part of the Government. It has a great bearing on insurability and premium ratings for life insurance, as well as compensation paid out by health insurance companies. These and many other factors should serve only to emphasize the importance that should be attached to the diagnosis of rheumatic fever, which, therefore, should never be made except on the basis of very definitive criteria.

Meanwhile, in view of the available evidence, it is equally important that all patients with streptococcal infections be treated promptly with peni-

cillin and that it be administered in a manner to ensure a continuous penicillin effect for at least seven to ten days.

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BOSTON TUBERCULOSIS ASSOCIATION

Dr. Nathaniel K. Wood, in his presidential address delivered last March before the Boston Tuberculosis Association, summarized briefly the accomplishments of that organization in the nearly forty-seven years of its existence. In 1903, the year of its foundation, 1227 persons had died in Boston of tuberculosis, and no hospital or clinic existed for those who were sick.

In its first fifteen years the Association made great strides in the development of public opinion on the needs of the sick and the prevention of tuberculosis, and the city authorities were influenced to make plans for a sanatorium and clinic for tuberculous patients. Prior to the opening of the Boston Sanatorium in 1906 the Association operated a day camp and employed two nurses for the care of the sick in their homes; after its opening the day camp was closed, and a school of outdoor life for children was opened. This was later turned over to the city but was given up after a year.

Meanwhile, in 1908, Mr. George S. Mumford, treasurer of the Association, brought to the attention of Mr. James J. Prendergast the need for a temporary home for men on the waiting list for the state sanatorium at Rutland. Mr. Prendergast gave the Association a tract of land of 16 acres in Mattapan, and the Prendergast Camp was constructed and served its purpose for fourteen years.

Further activities followed, one upon another. In 1911 the Association assumed responsibility for the salary of a public-health nurse to visit patients discharged from state sanatoriums, a work that was eventually taken over by the Massachusetts Department of Public Health. Another development was the employment of Miss Frances Stern as a domestic-science visitor, from which a housekeeping center evolved with Miss Isabel Hyams as chairman. In the words of Miss Hyams, quoted from an old Scottish writer, "He that would be good, must be happy; and he that would be happy, must be healthy."

Prior to World War I the Association employed a public-health nurse to develop medical service in industries, and an occupational-therapy teacher for patients in the Boston Sanatorium. During the war, however, contributions fell off, and the Association was thought by many of its members to have outlived its usefulness. They were reckoning without John B. Hawes, 2d, who became president in 1921 and, aided by an active executive committee, many of whom were founders, began to rebuild the organization.

In 1925 the Association engaged Murray P. Horwood, Ph.D., professor of sanitary science at the Massachusetts Institute of Technology, to conduct a tuberculosis survey of Boston. As a result of the survey the Prendergast Camp became the Prendergast Preventorium for children, and a "sheltered shop" was opened to build up work tolerance in men and women who had recovered from tuberculosis but were unable to do full-time work. This shop, opened in 1930, represents an early development in organized rehabilitation.

Health education has been expanded to cover more than lectures and literature, x-ray service has been provided at minimum cost and the Association participated in the recent mass x-ray program with funds and personnel.

In the concluding words of Dr. Wood:

> The reason our Association has prospered is that we have done so much personal work with those afflicted with tuberculosis, and have held out to them a helping hand which no other agency has offered them . . . When we add together the numbers of people reached by us in this past year by word of mouth, radio, movies, and Christmas Seal Sale letters, bearing the information of what we offer in service, the total is over 300,000.

UNITED NATIONS INTERNATIONAL CHILDREN'S EMERGENCY FUND

THE United Nations International Children's Emergency Fund, whose need is constant, is again issuing a special appeal in the name of the twenty million children of the world who lack food, clothing and medical care.

Established by the General Assembly of the United Nations in 1946, UNICEF has met with a uniformly generous response, which has enabled it to extend its help not only to the children of Europe, but to those of the Philippines, the Middle and Far East and Central and South America. At its inception the Congress of the United States appropriated $75,000,000 to be matched on a 72 to 28 per cent basis, the former from the United States, the latter from all other countries combined. In such a manner has this country, still productive and always generous, accepted a large share of the responsibility for the have nots of the world.

These children, who cannot otherwise be cared for, have been adopted by UNICEF; they, on the other hand, have adopted UNICEF as their symbol of the United Nations. Inquiries from those who find that their charity, begun at home, can be stretched to cover desperate needs abroad, should be addressed to the United Nations Children's Fund Committee, New York 16, New York.

The future of the world will soon be in the hands of this now helpless generation.

Medical knowledge, no more than any other knowledge, ever came by hereditary descent, or by inspiration; it is only by indomitable perseverance in the prosecution of other investigations of the phenomena of disease, that we are ever led to make any progress.

Boston M. & S. J., *June 26, 1850*

The *Journal* lacks extra copies of the February 2 and March 2, 1950, issues. If any subscribers who do not bind their copies have the above-mentioned issues on hand, the *Journal* will pay 15 cents for each copy left at or mailed to its office (8 Fenway, Boston 15).

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

HENDERSON — George D. Henderson, M.D., of Holyoke, died on June 14. He was in his seventy-sixth year.

Dr. Henderson received his degree from Western Reserve University School of Medicine in 1900. He was a former councilor of the Massachusetts Medical Society, was chief of the Medical Service at Holyoke Hospital and was a fellow of the American College of Physicians and American College of Surgeons.

His widow and a daughter survive.

ORCUTT — Wallace L. Orcutt, M.D., of Haverhill, died on June 7. He was in his sixty-seventh year.

Dr. Orcutt received his degree from Yale University School of Medicine in 1911. He was a member of the staff of Benson Hospital.

A son, a daughter and four brothers survive.

NEW HAMPSHIRE MEDICAL SOCIETY

REGARDING THE SEAL

The following data concerning the seal of the New Hampshire Medical Society displayed above have been taken from the records of the Society.

Exeter May 4, 1791 (First meeting of the Society)

"Voted, that Joshua Brackell, Ammi R. Cutter, Hall Jackson and John Jackson be the Committee, and that the aforsaid Committee be requested to Report a device of a Seal for the Society."

Dover 13th June, 1792

"Voted — That the Secretary (Sam' Tenney) procure an elegant engraving of the DEVISE OF A SEAL FOR THE SOCIETY reported to this meeting by the committee appointed for the purpose; which Devise is as follows — [Not given in record]"

Exeter May 21st 1794

"Resolved That the Corresponding Secretary shall get the Seal for this Society engraved on silver of three ounces weight, if it can be done in Boston for six pounds LM, but if it cannot be engraved in Boston for that price, to procure it in Europe of that weight."

No record has been found, to date, of the seal having been made or delivered to the Society. The earliest imprint that has been seen is on the license "to practice the following branches of Medicine — Practice of Medicine, Surgery and Obstetrics" issued on *October 13, 1887*, to Henry Onslow Smith, M.D., the father of the present secretary.

DEERING G. SMITH, M.D., *Secretary-Treasurer*

MISCELLANY

MASSACHUSETTS TRUDEAU SOCIETY

At a meeting of the Massachusetts Trudeau Society on June 8, the following officers were elected: president, Francis P. Dawson, Superintendent, Middlesex County Sanatorium, Waltham, Massachusetts; vice-president, John W. Strieder, 1180 Beacon Street, Brookline; secretary-treasurer, David Sherman, superintendent, Boston Sanatorium.

BOOK REVIEW

The Diagnosis and Treatment of Adrenal Insufficiency. By George W. Thorn, M.D. With the collaboration of Peter H. Forsham, M.D., M.A. (Cantab.). 8°, cloth, 171 pp., with 32 illustrations. Springfield, Illinois: Charles C Thomas, 1949. $5.50. American Lecture Series.

This monograph on adrenocortical insufficiency is a thorough compilation of the knowledge independently gained by the authors from careful clinical and investigative observations on a large number of patients with this condition.

The physiologic and chemical aspects of the adrenal gland are illustrated diagrammatically on the basis of present-day knowledge of steroid metabolism. Addison's disease is illuminatingly surveyed from the standpoint of the signs, symptoms and laboratory findings. Screening and tolerance tests, some based on newer methods as devised by the authors, are outlined, and careful interpretation of the results to be obtained is given. Of special practical significance is a five-day hospital diagnostic guide incorporating all the salient data desirable for determining adrenocortical function in any patient. A summary is given of all the currently available preparations of adrenocortical hormones, with a comment on their effectiveness, indications for their use and cost. The therapy of adrenal crisis and chronic adrenal insufficiency is described with equally practical insight.

Those already experienced with the problems of adrenal insufficiency will profit greatly from this monograph, as will those wishing to gain knowledge of the interesting problem of normal and pathologic adrenal physiology.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

An Atlas of the Blood and Bone Marrow. By R. Philip Custer, M.D., director, Laboratories of the Presbyterian Hospital in Philadelphia, assistant professor of pathology, University of Pennsylvania School of Medicine, and consultant to the Armed Forces Institute of Pathology. 4°, cloth, 321 pp., with 285 illustrations. Philadelphia: W. B. Saunders Company, 1949. $15.00.

This new atlas has been planned for the use of clinicians, hematologists, pathologists and medical technicians. The general aim of the book is to promote accuracy in diagnosis. The illustrations are unusual since they represent photomicrographs of relatively large microfields at high magnification, a better medium for comparison than water-color drawings of blood and marrow cells, and photomicrographs of sectioned bone marrow have been given in addition to smears. The atlas is divided into two parts, a preliminary one of three chapters on the hemolytopoietic system, and a large one of fourteen chapters on disorders of the blood and bone marrow. The work is based on the author's experience of eighteen years in the field of hematology. Except for the erythrocytic series, the recently standardized nomenclature is used. The atlas is well published and should be in all reference collections on the subject.

Secretory Mechanism of the Digestive Glands. By B. P. Babkin, M.D., D.Sc., LL.D., F.R.S.C. Second edition, revised and enlarged. 8°, cloth, 1027 pp., with 233 illustrations. New York: Paul B. Hoeber, Incorporated, 1950. $20.00.

This second edition of a work first published in 1944 has been revised and brought up to date. New material includes the possible role of carbonic anhydrase in the process of formation of the hydrochloric acid by the parietal cells and studies on a patient with gastric fistula and on the specific action of histamine on the parietal cells. More than two hundred and sixty new experimental investigations appearing since the publication of the first edition have been reviewed and discussed. Sections have been added on the effect on the secretory activity of the gastric glands of pilocarpine, acetylcholine, and caffeine; on the inhibition of gastric secretory activity by different methods; on pancreozymine; on antagonistic and synergistic phenomena in the autonomic nervous system; on secretory-inhibitory nerves; and on nervous and hormonal regulation of the pancreatic secretion. A comprehensive bibliography of 101 pages is appended to the text. There are indexes of authors and subjects. The book is well published in every way and is recommended for all medical libraries and all persons interested in the subject.

Osler, as a Gastroenterologist. By Felix Cunha, M.D. 8°, cloth, 57 pp., with a frontispiece. Alameda, California: Times-Starr Press, 1948. Privately printed.

In this historical monograph Dr. Cunha discusses the various published papers of Dr. Osler on disorders of the digestive tract. The first publication of Osler was nonmedical and was entitled "Christmas and the Microscope." It was published in *Hardwicke's Science Gossip* for February, 1869, and is reproduced in this monograph. The publishing is excellent, and the volume should be in all collections on medical history.

Intestinal Intubation. By Meyer O. Cantor, M.S., M.D., assistant attending surgeon, Grace Hospital, Detroit. 8°, cloth, 333 pp., with 147 illustrations. Springfield, Illinois: Charles C Thomas, 1949. $7.50.

In this special monograph Dr. Cantor discusses the use of tubes in the treatment of intestinal obstruction. He describes the tube known by his name and other tubes. The subject is thoroughly covered, and a list of selected references is appended to each chapter. In addition, a long bibliography of thirty-two pages is appended to the text. There are good indexes of authors and subjects. The monograph is recommended for all collections on gastroenterology.

Principles and Practice of Therapeutic Exercises. By Hans Kraus, M.D., assistant clinical professor of rehabilitation and physical medicine, New York University College of Medicine, and physician-in-charge of therapeutic exercise, Institute of Rehabilitation and Physical Medicine, New York University–Bellevue Medical Center. 8°, cloth, 309 pp., with 94 illustrations by Richard Kroth. Springfield, Illinois: Charles C Thomas, 1949. $6.50.

This book presents in simple form the fundamental knowledge of exercise therapy and its practical application. The text is divided into three sections: fundamental working principles, stressing the problems of local exercises; the application of therapeutic exercises to particular fields, including musculoskeletal conditions, the nervous system and respiration; and general exercises, in which it is only possible to give a brief outline of the whole field. A bibliography of selected references concludes the text. The book is well published, and it is a delight to find such a good, large type on nonglare paper. The volume is recommended for all collections on the subject.

NOTICES

Dr. James A. Lamphier announces the removal of his office to 47 Bay State Road, Boston, for the practice of obstetrics and gynecology.

NEW ENGLAND HOSPITAL FOR WOMEN AND CHILDREN

The monthly clinical conference and meeting of the staff will be held in the conference room on Thursday, July 6, at 7:15 p.m. Drs. Annella Brown and Constance Curtiss will discuss the subject "Some Practical Aspects of Fluid Balance in the Postoperative Patient."

(*Notices concluded on page xi*)

NOTICES (*Concluded from page 1030*)

AMERICAN COLLEGE OF SURGEONS

The thirty-sixth clinical congress of the American College of Surgeons will be held in Boston, October 23-27. Twenty-four hospitals in Boston and the vicinity will hold operative clinics for the visiting surgeons during the week. A special feature will be color television of surgical procedures from the Massachusetts General Hospital to the auditorium in Mechanics Hall. Official meetings, scientific sessions, medical motion pictures, a large technical exhibit and the twenty-ninth annual Hospital Standardization Conference will be other features of the meeting. Hotel headquarters will be at the Hotel Statler and the Copley Plaza.

SOCIETY MEETINGS AND CONFERENCES

JANUARY 9–DECEMBER 1. Laboratory Courses at Communicable Disease Center, Atlanta, Georgia. Page 950, issue of December 8.

JULY 2–5. American Proctologic Society. Page 848, issue of May 25.

JULY 3. Brazilian Society of Cardiology. Page 886, issue of June 1.

JULY 6. New England Hospital for Women and Children. Page 1030.

JULY 17–22. International Congress for Scientific Research. Page xvii, issue of September 1.

AUGUST 21–26. International Society of Hematology. Page 888, issue of December 1.

AUGUST 28–SEPTEMBER 1. American Congress of Physical Medicine. Page 428, issue of March 16.

AUGUST 31–SEPTEMBER 7. World Federation for Mental Health. Page 306, issue of February 23.

SEPTEMBER 3–9. International Heart Congress. Page 160, issue of January 26.

SEPTEMBER 7–9. All-Austrian Congress of Physicians. Page 994, issue of June 22.

SEPTEMBER 14. Progress in the Management of Hand Injuries. Dr. Henry E. Marble. Pentucket Association of Physicians. 8:30 p.m. Haverhill.

SEPTEMBER 27–29. Mississippi Valley Medical Society. Page 991, issue of December 15.

OCTOBER 12–14. American Association of Blood Banks. Page 428, issue of March 16.

OCTOBER 14–19. American Academy of Pediatrics. Page 962, issue of June 15.

OCTOBER 23–27. American College of Surgeons. Notice above.

NOVEMBER 1. New England Obstetrical and Gynecological Society. Hotel Somerset, Boston.

JANUARY 31. American Academy of Orthopaedic Surgery (see Kappa Delta Award for Research in Orthopedic Surgery). Page 736, issue of May 4.

APRIL 9–13. American College of Physicians. Page 962, issue of June 15.

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, JULY 6

THURSDAY, JULY 6

*9:00–10:00 a.m. Cardiac Grand Rounds. Main Amphitheater, Children's Medical Center.

7:15 p.m. Clinical Conference and Staff Meeting. New England Hospital for Women and Children.

FRIDAY, JULY 7

*9:00 a.m.–12:00 m. Combined Medical and Surgical Staff Rounds. Peter Bent Brigham Hospital

*10:00 a.m. Surgical Clinic. South End Health Unit, 57 East Concord Street, Boston.

*1:30 p.m. Tumor Clinic. Out-Patient Department. Mount Auburn Hospital, Cambridge.

MONDAY, JULY 10

*11:30 a.m.–12:15 p.m. Clinical Conference. South End Health Unit, 57 East Concord Street, Boston. Dr. Cleaveland Floyd in charge.

*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.

TUESDAY, JULY 11

*12:15–1:15 p.m. Clinicoroentgenological Conference. Peter Bent Brigham Hospital.

*1:30–2:30 p.m. Pediatric Rounds. Burnham Memorial Hospital for Children, Massachusetts General Hospital.

WEDNESDAY, JULY 12

*11:00 a.m.–12:00 m. Medical Rounds. Children's Medical Center.

*12:00 m. Clinicopathological Conference. Margaret Jewett Hall, Mount Auburn Hospital, Cambridge.

*12:00 m.–1:00 p.m. Clinicopathological Conference (Children's Medical Center). Amphitheater, Peter Bent Brigham Hospital.

*2:00–3:00 p.m. Combined Clinic of all Medical Center Services. Amphitheater, Children's Hospital.

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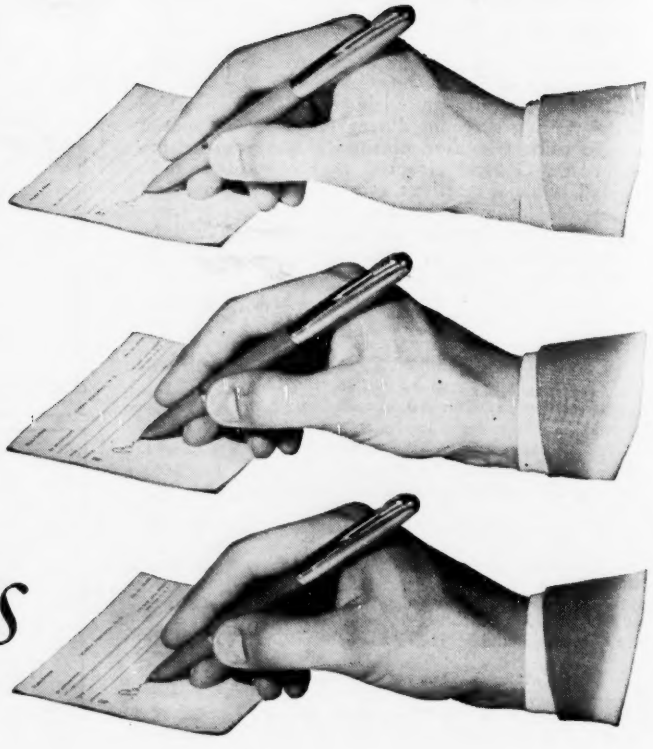

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